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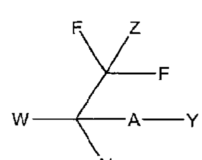
(54) Title: LXR MODULATORS



(I)

(57) Abstract: The present invention relates to methods for treatment of certain diseases or conditions mediated by Liver X Receptor (LXR) by the administration of a composition containing as an active ingredient a compound according to Formula (I). In particular, the invention relates to methods for treatment of cardiovascular diseases and atherosclerosis through the administration of a compound which modulates LXR activity.

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LXR MODULATORS

FIELD OF THE INVENTION

The present invention relates to methods for treatment of certain diseases or conditions mediated by Liver X Receptor (LXR) by the administration of a composition containing as an active ingredient a compound according to Formula I. In particular, the invention relates to methods for treatment of cardiovascular diseases and atherosclerosis through the administration of a compound which modulates LXR activity.

BACKGROUND

Liver X receptors (LXRs), LXRα and LXRβ, are nuclear receptors that regulate the expression of cytochrome P450 7A (CYP7A1), and thus the metabolism of several important lipids, including cholesterol and bile acids. LXRs were first identified as orphan members of the nuclear receptor superfamily (Song et al., *Proc. Natl. Acad. Sci.* **191**:10809-10813 (1994). Willy et al., *Gene Deve.* **9**:1033-1045 (1995)). The identification of a specific class of oxidized derivatives of cholesterol (oxysterol) as ligands for the LXRs, in combination with the description of an LXR response element in the promoter of the rat cholesterol 7α-hydroxylase genes, suggested that LXRs play an important role in the regulation of cholesterol homeostasis. Additional support for this role came from the analysis of LXRα-deficient mice (LXRα-/-), which uncovered the dysregulation of the CYP7A1 gene and several other important lipid-associated genes (Peet et al., *Curr. Opin. Genet. Dev.* **8**: 571-575 (1998)). Studies utilizing these animals confirmed the essential function of LXRα as a major sensor of dietary cholesterol and an activator of the bile acid synthetic pathway in mice. LXRα is expressed most highly in the liver and to a lesser extent in the kidney, small intestine, spleen and adrenal gland. On the contrary, LXRβ is ubiquitously expressed.

Naturally occurring or synthetic oxysterols such as 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 24(S),25-epoxycholesterol are believed to be transcriptional activators of LXRα and β. These oxysterols exist at concentrations that activate LXRs in tissues (e.g. liver, brain and

placenta) where both cholesterol metabolism and LXR expression are high. In human monocyte-derived macrophages by cholesterol loading, it was demonstrated a dose-dependent induction of ABCA1 and ABCG1 genes, suggesting that 27-hydroxycholesterol is an endogenous ligand for LXRs (Fu et al., *J. Biol. Chem.* **276**:38378-38387(2001)).

LXRs bind to the ATP binding cassette transporter-1 (ABCA1) gene promoter and increases expression of the gene to result in increased ABCA1 protein. ABCA1 is a membrane bound transport protein which is involved in the regulation of cholesterol efflux from extrahepatic cells onto nascent HDL particles. Humans with mutations in the gene ABCA1 have low levels of high density lipoprotein (HDL) and a concomitant increased risk of cardiovascular diseases such as atherosclerosis, myocardial infarction and ischemic stroke (Brooks-Wilson et al, *Nat. Genet.* **22**: 336-345 (1999), Bodzioch et al., *Nat. Genet.* **22**: 347-351(1999); and Rust et al., *Nat. Genet.* **22**: 352-355 (1999)). LXRα and β agonists were demonstrated to increase ABCA1 gene expression which resulted in increased HDL cholesterol, and decreased absorption of cholesterol and thereby decreased the risk of cardiovascular diseases (Sparrow et al., *J. Biol. Chem.* **277**:10021-10027 (2002).

LXRs signaling pathways play a central role in the control of macrophage cholesterol efflux through the coordinate regulation of ABCA1 and ABCG1 and surface constituent of plasma lipoprotein apolipoprotein E (apoE) gene expression. Recently, it was demonstrated that LXR/RXR heterodimers regulate apoE transcription directly, through interaction with a conserved LXR response element present in both ME.1 and ME.2. The ability of oxysterol and synthetic ligands to regulate apoE expression in adipose tissue and peritoneal macrophages is reduced in LXRα-/- or LXRβ-/- mice and abolished in double knockouts.

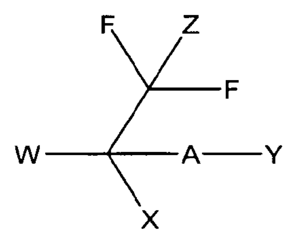
LXRs also play an important role in fatty acid metabolism by activating the sterol regulatory element-binding protein-1c (SREBP-1c) gene (Tobin, et al., *J. Biol. Chem.* **277**:10691-10697 (2002). In rodent liver and hepatoma cells, transcription of the SREBP-1c gene is stimulated by naturally occurring oxysterols, like 24(S),25-expoxycholesterol and 22(R)-hydroxycholesterol, that bind to LXRα and β. LXRs are also activated by T0901317, a synthetic

nonsteroidal compound. The level of SREBP-1c mRNA declined dramatically when cultured rat hepatoma cells were treated with inhibitors of 3-hydroxy-3-methylglutaryl coenzyme reductase, which block the synthesis of endogenous LXR ligands. This inhibition was reversed when the cells were incubated with either T0901317 or mevalonate, the product of the reductase reaction. These data indicated that basal transcription of the SREBP-1c gene requires an endogenous sterol that activates LXRs (Laffitte et al., *Proc. Natl. Acad. Sci.* **98**: 507-512 (2001)).

Accordingly, compounds which function as LXR modulaots would be useful in methods of increasing ABCA1, SREBP-1c, and apoE expression, increasing HDL cholesterol and treating LXR mediated diseases or conditions such as hypercholesterolemia and cardiovascular diseases.

SUMMARY OF THE INVENTION

The present invention related to compounds of the following general structure (I):



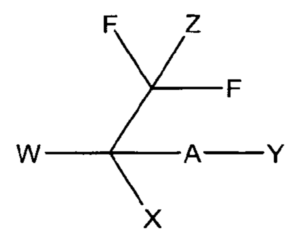
(I)

as well as prodrugs thereof, and pharmaceutically acceptable salts, wherein A, W, X, Y, and Z are as defined below. Other aspects of this invention will become apparent as the description of this invention continues. Hence, the foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way.

DETAILED DESCRIPTION OF THE INVENTION

The detailed description of the invention that follows is not intended to be exhaustive or to limit the invention to the precise details disclosed. It has been chosen and described to best explain the details of the invention to others skilled in the art.

The present invention related to compounds of the following general structure (I):

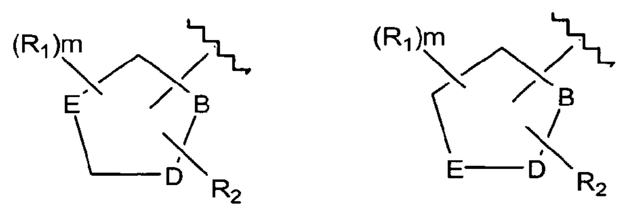


(I)

wherein

W is independently chosen from:

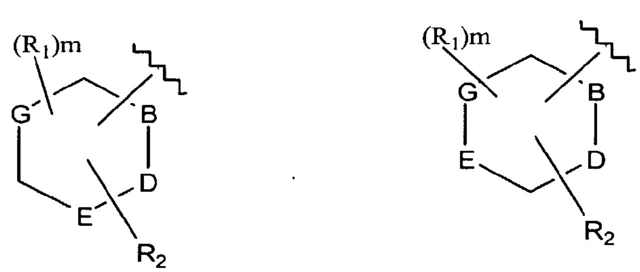
a five membered substituted non-aromatic heterocyclic ring containing one double bond having the following formulae (I a) and (I b):



I a I b

wherein B, D and E represent atoms selected from C, N, O or S;

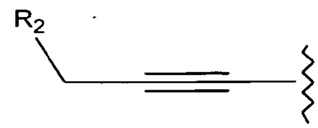
a six membered substituted non-aromatic heterocyclic ring containing zero to two double bonds having the following formulae (I c) and (I d):



I c I d

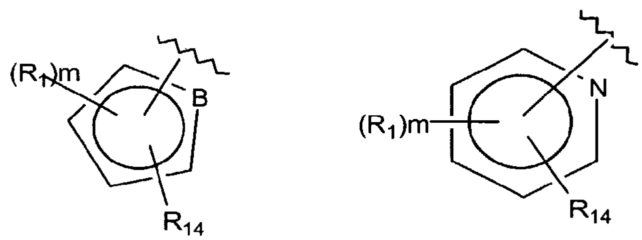
wherein B, D , E and G represent atoms selected from C, N, O or S;

an alkynyl group having the following formula (I e):



I e

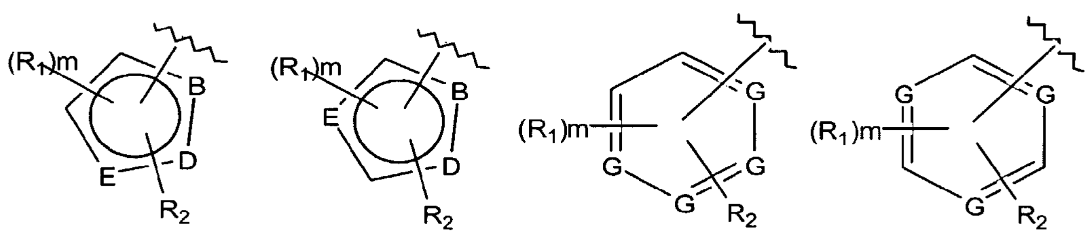
a five or six membered substituted aromatic heterocyclic ring having one heteroatom of the following formulae (II a) and (II b):



II a II b

a five or six membered substituted aromatic heterocyclic ring having at least two heteroatoms of the formulae (II c) ,(II d), (II e) and (II f) with the

proviso that (II c) and (II d) do not include the pyrazole ring:



II c II d II e II f

wherein D , E and B represent atoms selected from C, N, O or S, and G represents atoms selected from C or N ;

R_1 is independently chosen from halo, haloalkyl, hydroxy, thiol, substituted thiol, sulfonyl, sulfinyl, nitro, cyano, amino, substituted amino, C_1-C_6 alkyl and C_1-C_6 alkoxy, and when R_1 is hydroxy, C_1-C_6 alkoxy, thiol, substituted thiol,

amino, substituted amino, or C_1-C_6 alkyl, such radical may be combined with R_2 or R_{14} to form a ring of 5-7 members when R_1 is positioned next to R_2 or R_{14};

R_2 is selected from $-N(R_3)C(O)R_4$, $-C(O)NR_4R_5$, $-N(R_3)C(O)NR_4R_5$, $N(R_3)SO_2R_7$, $-N(R_3)SO_2NR_4R_3$, $-N(R_3)C(O)OR_4$, $-C(O)OR_4$, $-C(S)OR_4$, $-SR_3$, Phenyl, $-N(R_3)C(S)NR_4R_5$, $-NR_3R_4$,$-N(R_3)C(=NR_3)NR_4R_5$, $-N(R_3)C(=NCN)NR_4R_5$, $-N(R_3)C(=CHNO_2)NR_4R_5$, $-NR_3P(O)R_4R_5$, $-NR_3P(O)(OR_4)(OR_5)$, $-NR_3P(O)(OR_4)(NR_5)$, $-N(R_3)P(O)(NR_4)(NR_5)$, $-N(R_3)C(=NR_3)R_6$, $-COR_6$, $-C(R_6)(OH)R_7$, $-C(R_8)=NOR_4$, $-C(R_8)=NR_3$, $-C(R_8)=NNR_4R_5$, $-SOR_7$, $-SO_2R_7$, $-P(O)(OR_4)(OR_5)$, $-P(O)(R_4)(R_5)$,$-P(O)(OR_4)(OR_5)$ $-P(O)(NR_3)(OR_4)$, $-P(O)(NR_4)(NR_5)$, a 3-7 membered ring containing from zero to three heteroatoms selected from O, N, or S, which may be substituted by R_9, R_{10}, R_{11}, R_{12} or R_{13}, or may be combined with R_1 to form a ring of 5-7 members when R_1 is positioned next to R_2;

R_3 is hydrogen, alkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, acyl, or may form a ring of 5-7 members with R_4 or R_5;

R_4 is hydrogen, alkyl, aryl, heterocyclyl, acyl, or may form a ring of 5-7 members with R_5 or R_3;

R_5 is hydrogen, alkyl, aryl, or heterocyclyl, acyl or may form a ring of 5-7 members with R_3 or R_4;

R_6 and R_7 may be equal or different and are selected from hydrogen, alkyl, aryl, or heterocylcyl;

R_8 is hydrogen, alkyl, aryl, heterocylcyl, amino or substituted amino;

R_9, R_{10}, R_{11} and R_{12} may be equal or different and are selected from hydrogen, alkyl, aryl, heterocyclyl, nitro, cyano, carboxylic acid, ester, amides, halo, hydroxyl, amino, substituted amino, alkoxy, acyl, ureido, sulfonamido, sulfamido, sulfonyl, sulfinyl, or guanadinyl;

R_{13} is hydrogen, alkyl, aryl, ester, heterocyclyl, acyl, sulfonyl, ureido, or guanadinyl;

R_{14} is selected from $-NR_3C(S)NR_4R_5$, $-NR_3C(=NR_3)NR_4R_5$, $-NR_3C(=NCN)NR_4R_5$, $-NR_3C(=CHNO_2)NR_4R_5$, $-NR_3P(O)R_4R_5$, $-NR_3P(O)(OR_4)(OR_5)$, $-NR_3P(O)(OR_4)(NR_5)$, $-NR_3P(O)(NR_4)(NR_5)$, $-NR_3C(=NR_3)R_6$, $-COR_6$, $-C(R_6)(OH)R_7$, $-C(R_8)=NOR_4$, $-C(R_8)=NR_3$, $-C(R_8)=NNR_4R_5$, SOR_7, $-SO_2R_7$,

-P(O)(OR$_4$)(OR$_5$), -P(O)(R$_4$)(R$_5$), -P(O)(OR$_4$)(OR$_5$), -P(O)(NR$_3$)(OR$_4$), -P(O)(NR$_4$)(NR$_5$), a 3-7 membered ring containing from zero to three heteroatoms selected from O, N, or S, which may be substituted by R$_9$, R$_{10}$, R$_{11}$, R$_{12}$ or R$_{13}$, or may be combined with R$_1$ to form a ring of 5-7 members when R$_1$ is positioned next to R$_{14}$;

A is O, S, or NR$_3$;

m is from zero to three;

X is H, CF$_2$Z, or CF$_3$, or together with Y forms a double bond when A is O;

Y is hydrogen, or together with X forms a double bond when A is O;

Z is F, Br, Cl, I or CF$_3$;

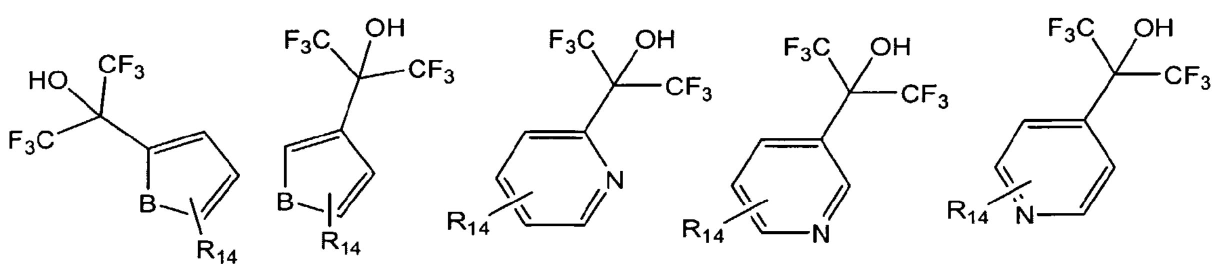
the corresponding enantiomers, diastereoisomers or tautomers, or a pharmaceutically acceptable salt, or a prodrug thereof in a pharmaceutically-acceptable carrier.

According to the present invention, there are several preferred embodiments which are described more fully below,

A preferred embodiment of the present invention relates to those compounds (I) wherein X is CF$_3$; Y is hydrogen; and Z is F.

Another preferred embodiment of the present invention relates to those compounds (I), wherein R$_1$ is hydrogen.

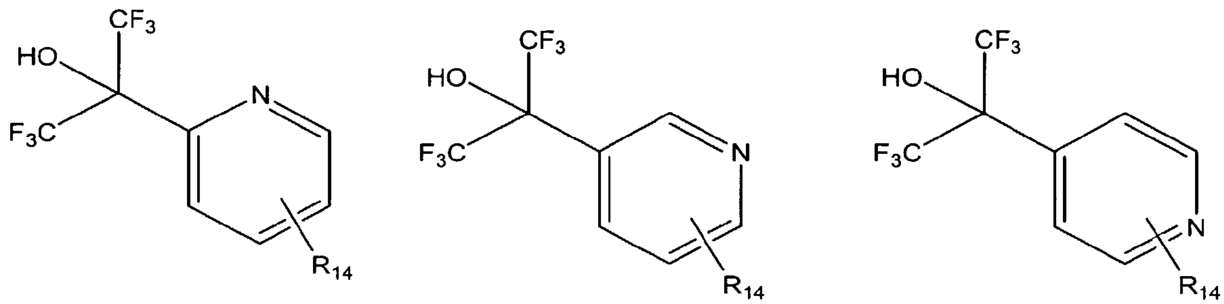
Still another preferred embodiment of the present invention relates to those compounds (I), wherein W is selected from a five or six membered substituted aromatic heterocyclic ring containing one heteroatom and having the following formulae:



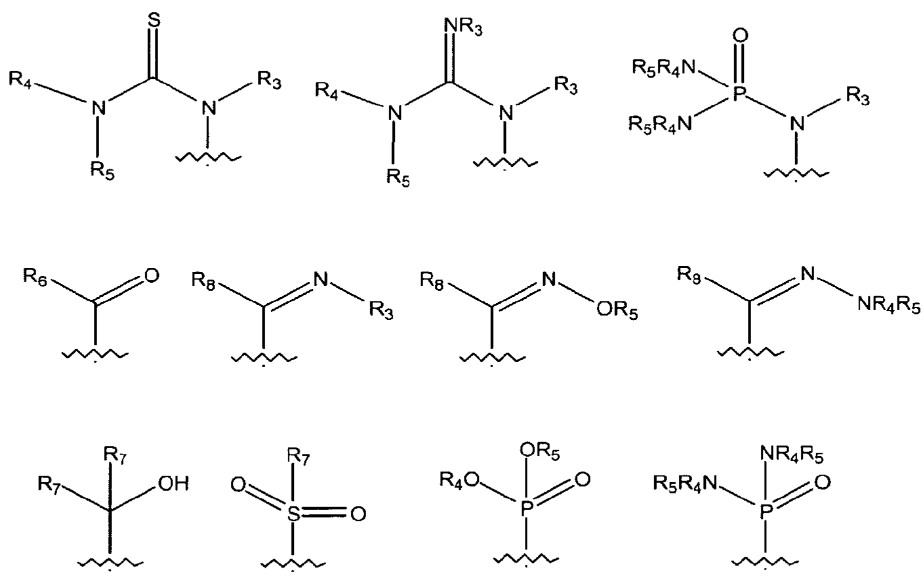
II g II h II i II j II k

wherein B is selected from N, O or S and R$_{14}$ is as defined above.

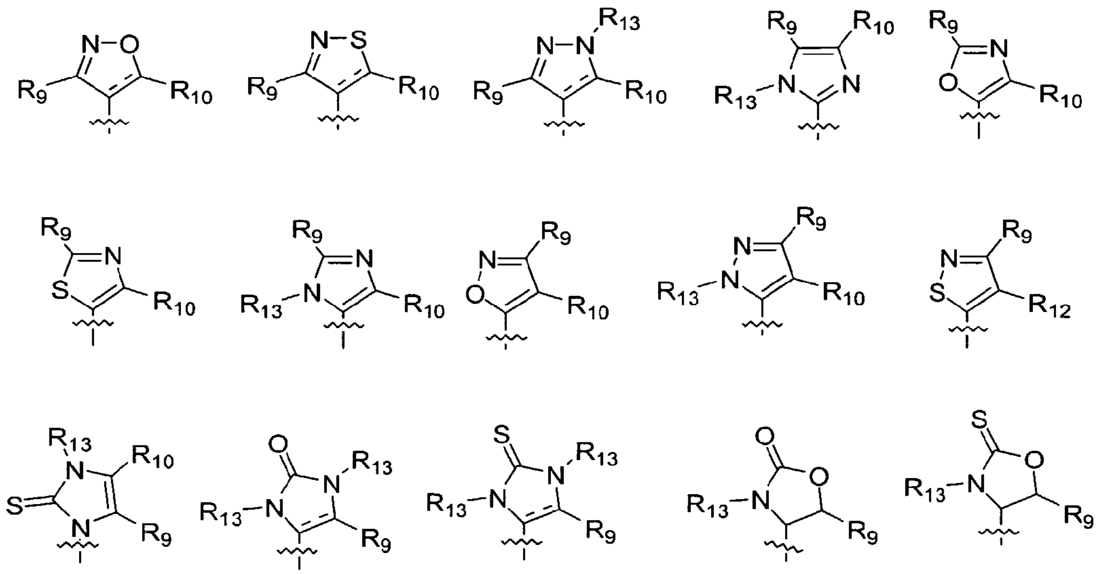
Amongst compounds (II g), (II h), (II i), (II j) and (II k), most preferred is pyridyl of the formulae:



Yet another preferred embodiment of the present invention relates to those compounds (II g), (II h), (II i), (II j) and (II k) wherein R_{14} is selected from the following groups:

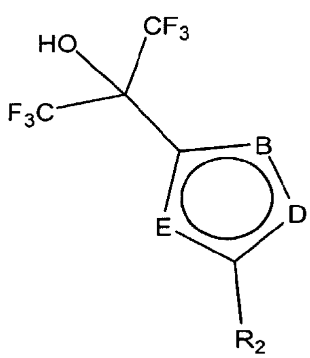


or

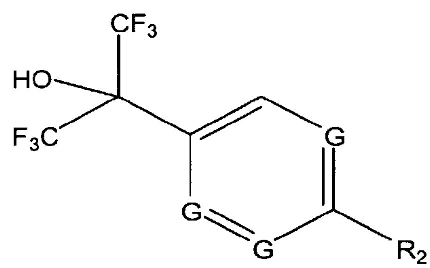


wherein R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} and R_{13} are as defined above.

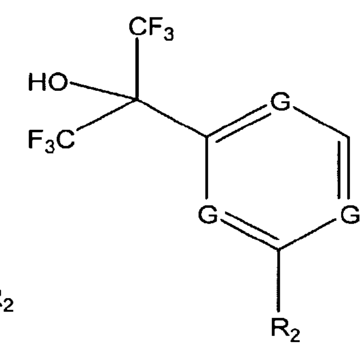
Still another preferred embodiment of the present invention relates to those compounds (I) wherein W is a five or six membered substituted aromatic heterocyclic ring containing at least two heteroatoms with the proviso that the pyrazole ring is not included and having the following formulae (II m), (II n) and (II o):



II m



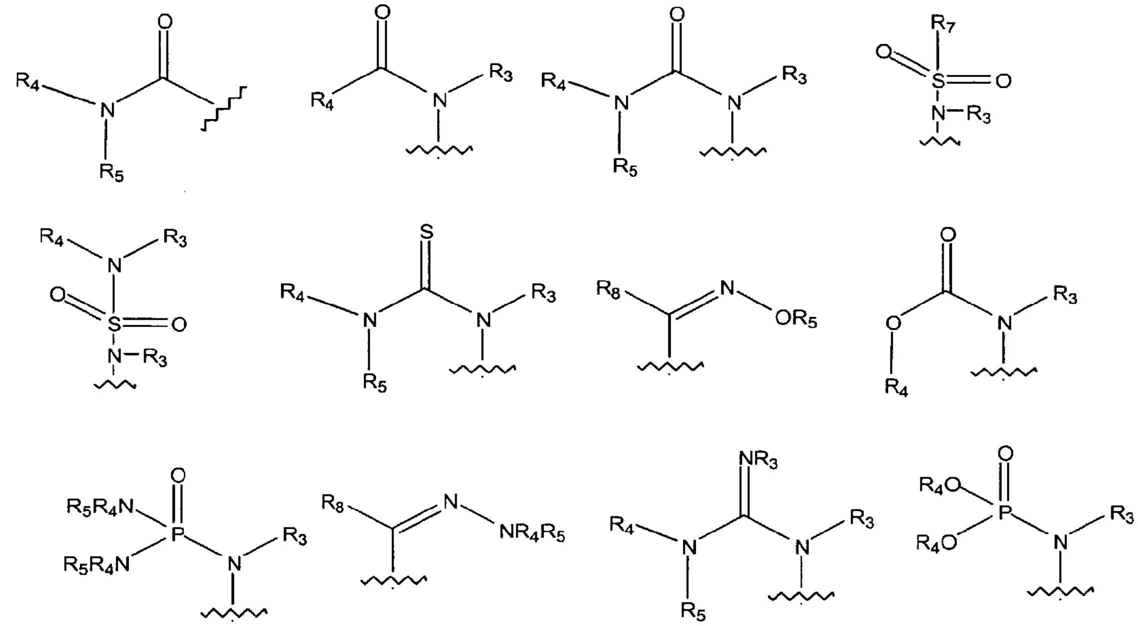
II n



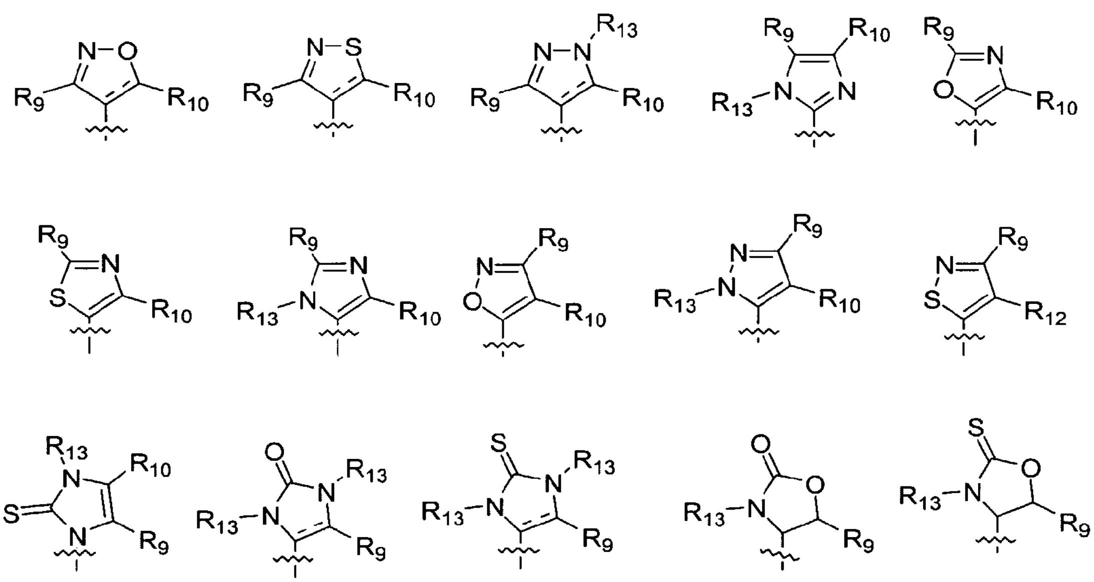
II o

Wherein R_2 is as defined as above and D , E and B represent atoms selected from C, N, O or S, and G represents atoms selected from C or N;

Yet another preferred embodiment of the present invention relates to those compounds (II m), (II n) and (II o), wherein R_2 is chosen from the following groups:

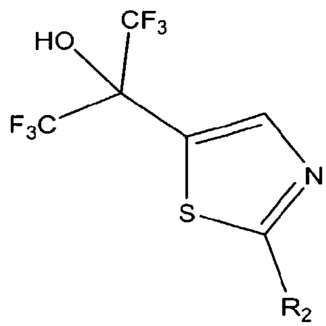


or



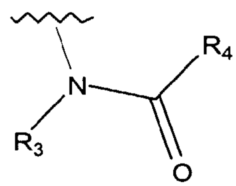
wherein R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} and R_{13} are as defined above.

Amongst compounds (II m), (II n) and (II o) of five or six membered substituted aromatic heterocyclic ring containing at least two heteroatoms, the most preferred for W is a substituted thiazole of the formula (II p):



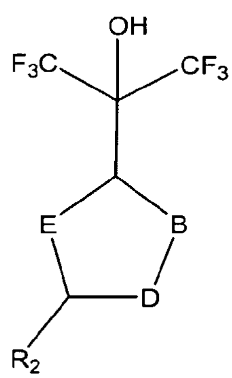
(II p)

In which R_2 is more preferably chosen from following group:



wherein most preferably R_4 is chosen from substituted aryl and R_3 is chosen from substituted arylalkyl;

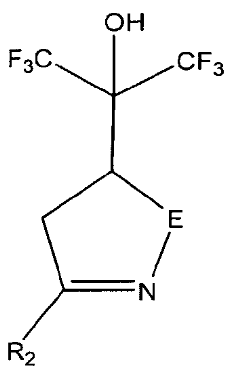
Still another preferred embodiment of the present invention relates to those compounds (I), wherein W is chosen from a five membered substituted non-aromatic heterocyclic ring containing one double bond and having the following formula:



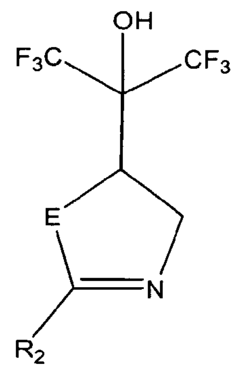
I f

Wherein at least one of B, D and E represents a heteroatom selected from O, S and N;

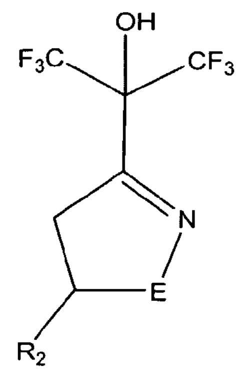
Amongst compounds (I f), the preferred five numbered substituted non-aromatic heterocyclic rings have the following formulae:



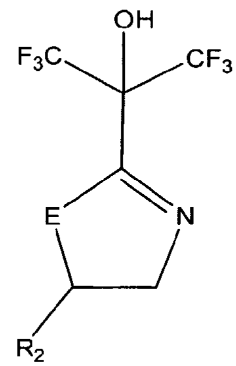
I g



I h

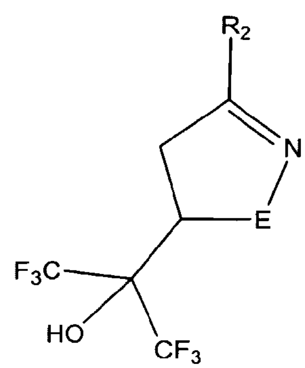


I i



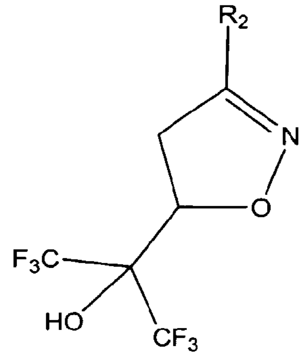
I j

Amongst above compounds (I g), (I h), (I i) and (I j), a more preferred non-aromatic heterocyclic ring has the following formula, wherein E represents a hetero atom selected from O, S or N:



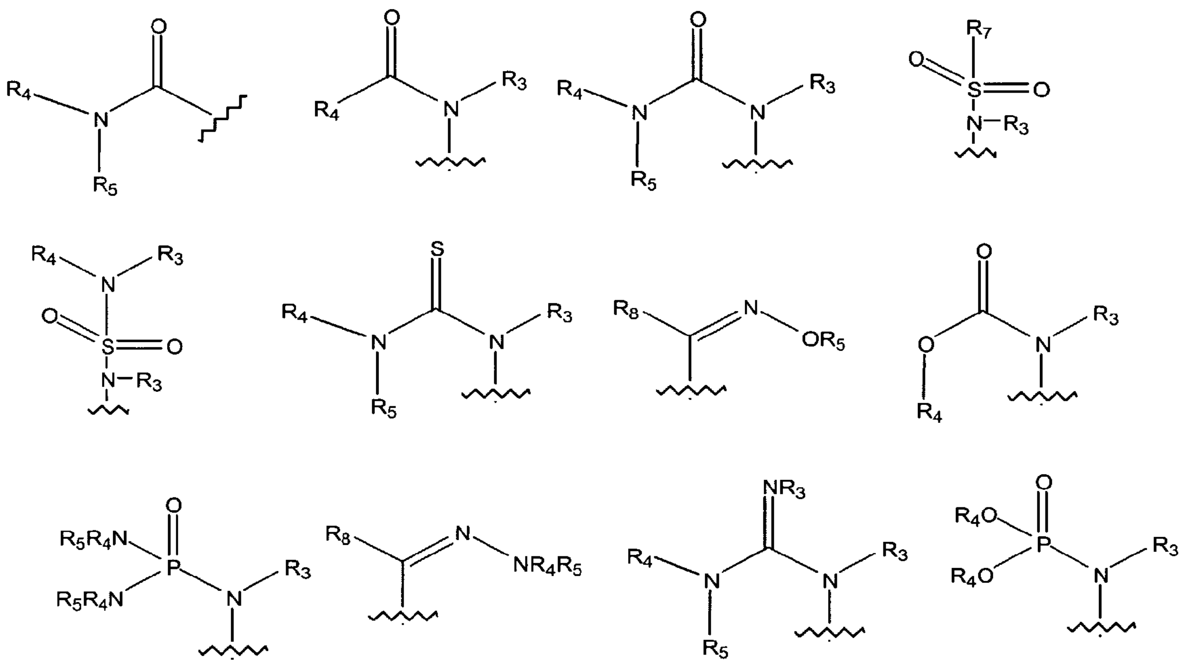
I k

The most preferred non-aromatic heterocyclic ring has the following formula:

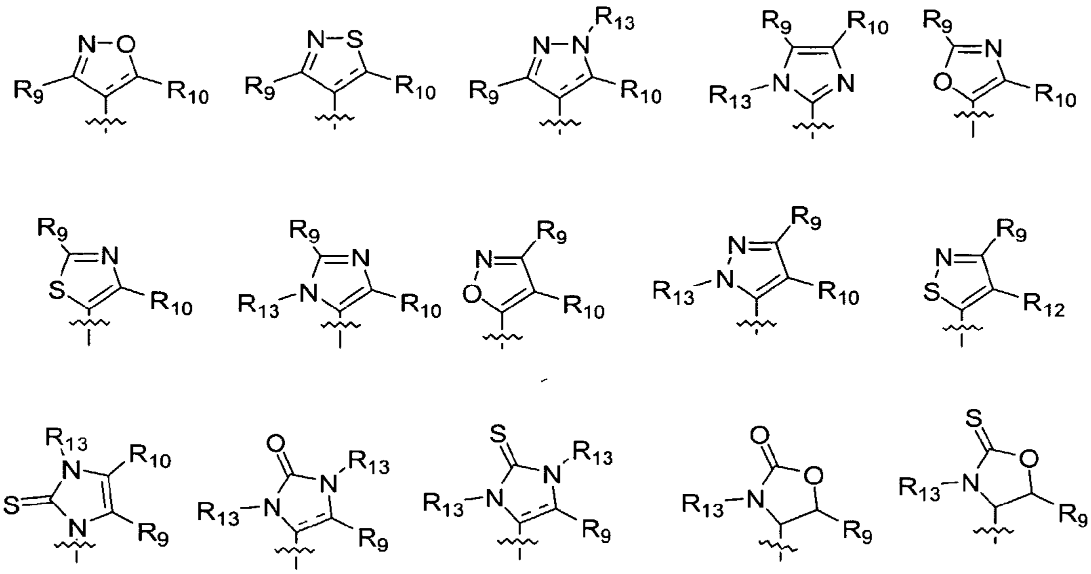


I m

wherein R_2 is preferably selected from the following groups:

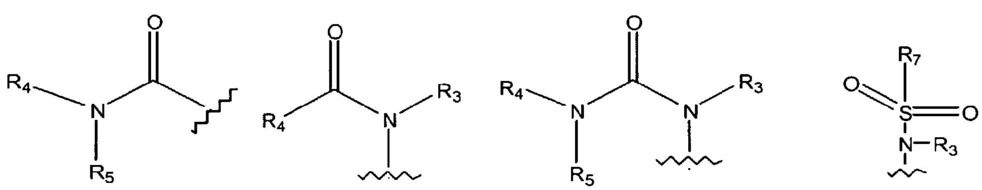


or



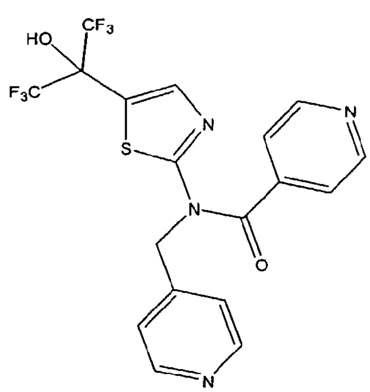
wherein R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} and R_{13} are as defined above.

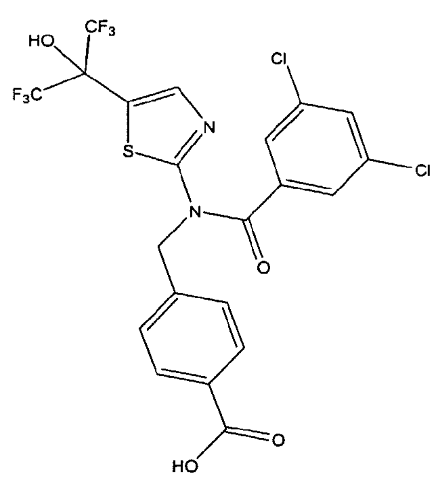
Amongst above R_2 groups of compound (I m), most preferred are the following:



wherein R_3, R_4, R_5, and R_7 are as defined above.

Exemplary of the compounds of this invention (I) are:





DEFINITIONS

As used herein, "alkyl" means a cyclic, branched, or straight chain chemical group containing only carbon and hydrogen, such as methyl, pentyl, and adamantyl. Alkyl groups can either be unsubstituted or substituted with one or more substituents, e.g., halogen, alkoxy, acyloxy, amino, amido, cyano, nitro, hydroxyl, mercapto, carboxy, carbonyl, benzyloxy, aryl, heteroaryl, or other functionality that may be suitably blocked, if necessary for purposes of the invention, with a protecting group. Alkyl groups can be saturated or unsaturated (e.g., containing -C=C- or -C≡C- subunits), at one or several positions. Typically, alkyl groups will comprise 1 to 12 carbon atoms, preferably 1 to 10, and more preferably 1 to 8 carbon atoms or cyclic groups containing three to eight carbons.

As used herein, "lower alkyl" means a subset of alkyl, and thus is a hydrocarbon substituent, which is linear, cyclic or branched. Preferred lower alkyls are of 1 to about 6 carbons, and may be branched or linear, and may include cyclic substituents, either as part or all of their structure. Examples of lower alkyl include butyl, propyl, isopropyl, ethyl, and methyl. Likewise, radicals using the terminology "lower" refer to radicals preferably with 1 to about 6 carbons in the alkyl portion of the radical.

As used herein, "amido" means a H-CON- or alkyl-CON-, aryl-CON- or heterocyclyl-CON group wherein the alkyl, aryl or heterocyclyl group is as herein described.

As used herein, "aryl" means a substituted or unsubstituted aromatic radical having a single-ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl), which can be optionally unsubstituted or substituted with amino, cyano, hydroxyl, lower alkyl, haloalkyl, alkoxy, nitro, halo, mercapto, and other substituents, and which may or may not include one or more heteroatoms. Preferred carbocyclic aryl is phenyl. The term "heteroaryl" is clearly contemplated in the term "aryl". Preferably where the term aryl represents a heterocycle, it is referred to as "heteroaryl", and has one or more heteroatom(s). Preferred are monocyclic heterocycles of 5 or 6 members. Hence preferred heteroaryl is a monovalent unsaturated aromatic group having a single ring and having at least one hetero atom, such as N, O, or S, within the ring, which can optionally be unsubstituted or substituted with amino, cyano, nitro, hydroxyl, alkyl,

haloalkyl, alkoxy, aryl, halo, mercapto, oxo (hence forming a carbonyl.) and other substituents. Examples of heteroaryl include thienyl, pyrridyl, furyl, oxazolyl, oxadiazolyl, pyrollyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl and others.

In this definition it is clearly contemplated that substitution on the aryl ring is within the scope of this invention. Where substitution occurs, the radical is called substituted aryl. Preferably one to three, more preferably one or two, and most preferably one substituent occur on the aryl ring. Preferred substitution patterns in five membered rings are substituted in the 2 position relative to the connection to the claimed molecule. Though many substituents will be useful, preferred substituents include those commonly found in aryl compounds, such as alkyl, hydroxy, alkoxy, cyano, nitro, halo, haloalkyl, mercapto and the like.

As used herein, “amide” includes both RNR’CO- (in the case of R = alkyl, alkaminocarbonyl-) and RCONR’- (in the case of R = alkyl, alkyl carbonylamino-).

As used herein, the term “ester” includes both ROCO- (in the case of R = alkyl, alkoxycarbonyl-) and RCOO- (in the case of R = alkyl, alkylcarbonyloxy-).

As used herein, "acyl" means an H-CO- or alkyl-CO-, aryl-CO- or heterocyclyl-CO- group wherein the alkyl, aryl or heterocyclcyl group is as herein described. Preferred acyls contain a lower alkyl. Exemplary alkyl acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, t-butylacetyl, butanoyl and palmitoyl.

As used herein, "halo" is a chloro, bromo, fluoro or iodo atom radical. Chloro, bromo and fluoro are preferred halides. The term “halo” also contemplates terms sometimes referred to as "halogen", or "halide".

As used herein, "haloalkyl" means a hydrocarbon substituent, which is linear or branched or cyclic alkyl, alkenyl or alkynyl substiuted with chloro, bromo, fluoro or iodo atom(s). Most preferred of these are fluoroalkyls, wherein one or more of the hydrogen atoms have been substituted by fluoro. Preferred haloalkyls are of 1 to about 5 carbons in length, More preferred haloalkyls are 1 to about 4 carbons, and most preferred are 1 to 3 carbons in length. The skilled artisan will recognize then that as used herein, "haloalkylene" means a diradical variant of haloalkyl, such diradicals may act as spacers between radicals, other

atoms, or between the parent ring and another functional group. For example, the linker CHF-CHF is a haloakylene diradical.

As used herein, “heterocyclyl” means heterocyclic radicals, which are saturated or unsaturated. These may be substituted or unsubstituted, and are attached to other via any available valence, preferably any available carbon or nitrogen. More preferred heterocycles are of 5 or 6 members. In six membered non-aromatic monocyclic heterocycles, the heteroatom(s) are selected from one up to three of O, N or S, and wherein when the heterocycle is five membered and non-aromatic, preferably it has one or two heteroatoms selected from O, N, or S.

As used herein, “substituted amino” means an amino radical which is substituted by one or two alkyl, aryl, or heterocyclyl groups, wherein the alkyl, aryl or heterocyclyl are defined as above.

As used herein, “substituted thiol” means RS- group wherein R is an alkyl, an aryl, or a heterocyclyl group, wherein the alkyl, aryl or heterocyclyl are defined as above.

As used herein, “sulfonyl” means an alkylSO_2, arylSO_2 or heterocyclyl-SO_2 group wherein the alkyl, aryl or heterocyclyl are defined as above.

As used herein, "sulfamido" means an alkyl-N-$S(O)_2$N-, aryl-N$S(O)_2$N- or heterocyclyl-N$S(O)_2$N- group wherein the alkyl, aryl or heterocyclcyl group is as herein described.

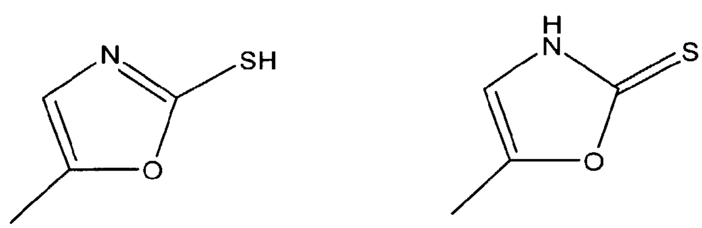
As used herein, "sulfonamido" means an alkyl-$S(O)_2$N-, aryl-$S(O)_2$N- or heterocyclyl- $S(O)_2$N- group wherein the alkyl, aryl or heterocyclcyl group is as herein described.

As used herein, "ureido" means an alkyl-NCON-, aryl-NCON- or heterocyclyl-NCON- group wherein the alkyl, aryl or heterocyclcyl group is as herein described

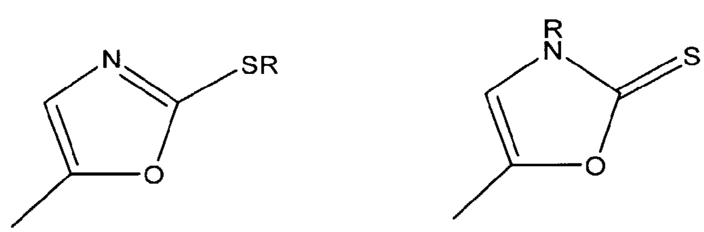
A used herein, a “radical” may form a ring with another radical as described herein. When such radicals are combined, the skilled artisan will understand that there are no unsatisfied valences in such a case, but that specific substitutions, for example a bond for a hydrogen, is made. Hence certain radicals can be described as forming rings together. The skilled artisan will recognize that such rings can and are readily formed by routine chemical

reactions, and it is within the purview of the skilled artisan to both envision such rings and the methods of their formations. Preferred are rings having from 3-7 members, more preferably 5 or 6 members. As used herein the term “ring” or “rings” when formed by the combination of two radicals refers to heterocyclic or carbocyclic radicals, and such radicals may be saturated, unsaturated, or aromatic. For example, preferred heterocyclic ring systems include heterocyclic rings, such as morpholinyl, piperdinyl, imidazolyl, pyrrolidinyl, and pyridyl.

The skilled artisan will recognize that some structures described herein may be resonance forms or tautomers of compounds that may be fairly represented by other chemical structures, even when kinetically, the artisan recognizes that such structures are only a very small portion of a sample of such compound(s). Such compounds are clearly contemplated within the scope of this invention, though such resonance forms or tautomers are not represented herein. For example,



the above substructures clearly represent the same radical and reference to either clearly contemplates the other. In addition, the following compounds may represent prodrugs when R can be removed by biological processes *in situ*:



Compounds and compositions herein also specifically contemplate pharmaceutically acceptable salts, whether cationic or anionic. A "pharmaceutically-acceptable salt" is an anionic salt formed at any acidic (e.g., carboxyl) group, or a cationic salt formed at any basic (e.g., amino) group. Many such salts are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein). Preferred counter-ions of salts formable

at acidic groups can include cations of salts, such as the alkali metal salts (such as sodium and potassium), and alkaline earth metal salts (such as magnesium and calcium) and organic salts. Preferred salts formable at basic sites include anions such as the halides (such as chloride salts). Of course, the skilled artisan is aware that a great number and variation of salts may be used, and examples exist in the literature of either organic or inorganic salts useful in this manner.

It is also clearly contemplated that compounds of the invention can be provided as biohydrolyzable prodrugs, as they are understood in the art. “Prodrug”, as used herein is any compound wherein when it is exposed to the biological processes in an organism, is hydrolyzed, metabolized, derivatized or the like, to yield an active substance having the desired activity. The skilled artisan will recognize that prodrugs may or may not have any activity as prodrugs. It is the intent that the prodrugs described herein have no deleterious effect on the subject to be treated when dosed in safe and effective amounts. These include for example, biohydrolyzable amides and esters. A "biohydrolyzable amide" is an amide compound which does not essentially interfere with the activity of the compound, or that is readily converted *in vivo* by a cell, tissue, or human, mammal, or animal subject to yield an active compound of the invention. A "biohydrolyzable ester" refers to an ester compound of the invention that does not interfere with the activity of these compounds or that is readily converted by an animal to yield an active formula (I) compound. Such biohydrolyzable prodrugs are understood by the skilled artisan and are embodied in regulatory guidelines.

Inasmuch as the compounds of the invention may contain optical centers, "optical isomer", "stereoisomer", "enantiomer," "diastereomer," as referred to herein have the standard art recognized meanings (cf. *Hawleys Condensed Chemical Dictionary*, 11th Ed.) and are included in the compounds claimed, whether as racemates, or their optical isomers, stereoisomers, enantiomers, diastereomers.

As used herein “cardiovascular diseases” include arrhthymia, atrial fibrillation, congestive heart failure, coronary artery disease, hypertension,

myocardial infarction, stroke, ventricular fibrillation, among others, particularly cardiovascular ischemia and those conditions modulated by LXR.

COMPOSITIONS

The compositions of the present invention comprise:

(a) a safe and effective amount of a LXR modulating compound (I), prodrug or pharmaceutical salt thereof; and

(b) a pharmaceutically-acceptable carrier.

As discussed above, numerous diseases can be mediated by LXR related therapy. Thus, the compounds of this invention are useful in therapy with regard to conditions involving this LXR activity.

Accordingly, the compounds of this invention can therefore be formulated into pharmaceutical compositions for use in prophylaxis, management and treatment of these conditions. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA.

A "safe and effective amount" of a compound of the present invention is an amount that is effective, to modulate LXR activity, in a subject, a tissue, or a cell, and preferably in an animal, more preferably in a mammal, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio, when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the duration of treatment, the nature of concurrent therapy (if any), the specific dosage form to be used, the carrier employed, the solubility of the compound therein, and the dosage regimen desired for the composition.

In addition to the subject compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of

the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration preferably to an animal, preferably mammal being treated.

Some examples of substances, which can serve as pharmaceutically-acceptable carriers or components thereof, are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

If the subject compound is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with blood-compatible suspending agent, the pH of which has been adjusted to about 7.4. In particular, pharmaceutically-acceptable carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

The compositions of this invention are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition of this invention containing an amount of a compound that is suitable for administration to an

animal, preferably mammal subject, in a single dose, according to good medical practice. (The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day, and are expected to be given more than once during a course of therapy, though a single administration is not specifically excluded. The skilled artisan will recognize that the formulation does not specifically contemplate the entire course of therapy and such decisions are left for those skilled in the art of treatment rather than formulation.) These compositions preferably contain from about 5 mg (milligrams), more preferably from about 10 mg to about 1000 mg, more preferably to about 500 mg, most preferably to about 300 mg, of the selected compound.

The compositions of this invention may be in any of a variety of forms, suitable (for example) for oral, nasal, rectal, topical (including transdermal), ocular, intracereberally, intravenous, intramuscular, or parenteral administration. (The skilled artisan will appreciate that oral and nasal compositions comprise compositions that are administered by inhalation, and made using available methodologies.) Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropies, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the inhibitory activity of the compound. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2d Edition (1976).

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25%

to about 50%, of the compound. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art.

Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid

compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

Compositions of the subject invention may optionally include other drug actives.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The compositions of this invention can also be administered topically to a subject, e.g., by the direct application or spreading of the composition on the epidermal or epithelial tissue of the subject, or transdermally via a "patch". Such compositions include, for example, lotions, creams, solutions, gels and solids. These topical compositions preferably comprise a safe and effective amount, usually at least about 0.1%, and preferably from about 1% to about 5%, of the compound. Suitable carriers for topical administration preferably remain in place on the skin as a continuous film, and resist being removed by perspiration or immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the compound. The carrier may include pharmaceutically-acceptable emolients, emulsifiers, thickening agents, solvents and the like.

METHODS OF ADMINISTRATION

The compounds and compositions of this invention can be administered topically or systemically. Systemic application includes any method of

introducing compound into the tissues of the body, e.g., intra-articular, intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual administration, inhalation, rectal, or oral administration. The compounds of the present invention are preferably administered orally.

The specific dosage of the compound to be administered, as well as the duration of treatment is to be individualized by the treating clinicians. Typically, for a human adult (weighing approximately 70 kilograms), from about 5 mg, preferably from about 10 mg to about 3000 mg, more preferably to about 1000 mg, more preferably to about 300 mg, of the selected compound is administered per day. It is understood that these dosage ranges are by way of example only, and that daily administration can be adjusted depending on the factors listed above.

In all of the foregoing, of course, the compounds of the invention can be administered alone or as mixtures, and the compositions may further include additional drugs or excipients as appropriate for the indication. For example, in the treatment of cardiovascular diseases, it is clearly contemplated that the invention may be used in conjunction with beta-blockers, calcium antagonists, ACE inhibitors, diuretics, angiotensin receptor inhibitors, or known cardiovascular drugs or therapies. Hence, in this example, novel compounds or compositions of this invention are useful when dosed together with another active and can be combined in a single dosage form or composition.

The composition can also be administered in the form of liposome delivery system, such as small unilamellar vesicles, large unilamellar vesicles, and mutilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphayidylcholines.

PREPARATION OF COMPOUNDS OF THE INVENTION

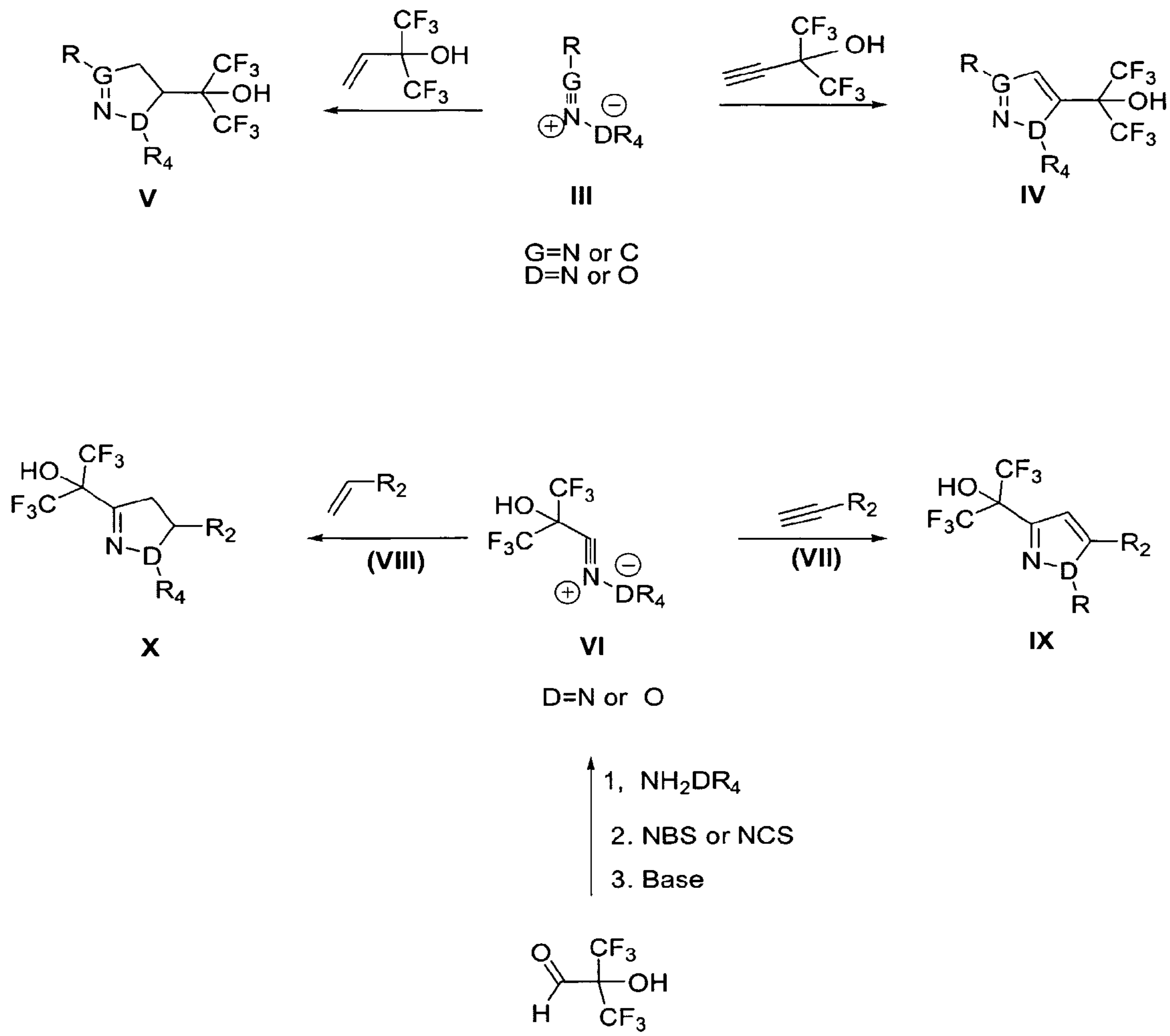
The starting materials used in preparing the compounds of the invention are known, made by known methods, or are commercially available. It will be apparent to the skilled artisan that methods for preparing precursors and functionality related to the compounds claimed herein are generally described in the literature. The skilled artisan given the literature and this disclosure is well equipped to prepare any of the claimed compounds.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out manipulations without further direction, that is, it is well within the scope and practice of the skilled artisan to carry out these manipulations. These include reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification and saponification and the like. These manipulations are discussed in standard texts such as March *Advanced Organic Chemistry* (Wiley), Carey and Sundberg, *Advanced Organic Chemistry* and the like.

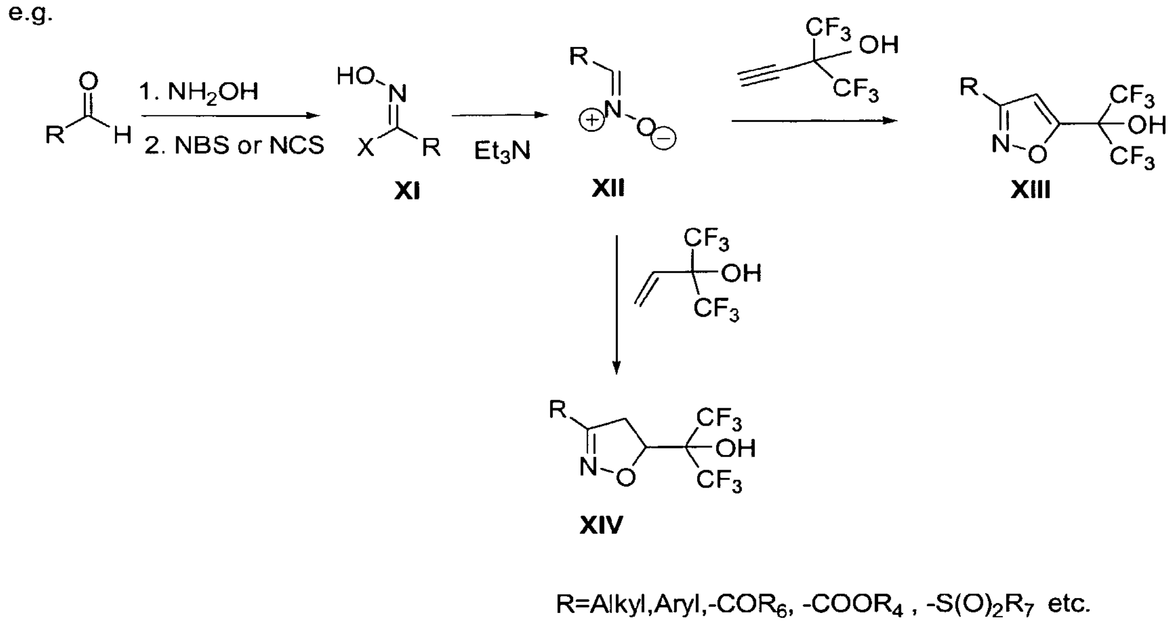
The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be found for example in T. Greene and P. Wuts *Protecting Groups in Organic Synthesis*, 2nd Ed., John Wiley & Sons (1991).

The following example schemes are provided for the guidance of the reader, and represent preferred methods for making the compounds exemplified herein. These methods are not limiting, and it will be apparent that other routes may be employed to prepare these compounds. Such methods specifically include solid phase based chemistries, including combinatorial chemistry. The skilled artisan is thoroughly equipped to prepare these compounds by those methods given the literature and this disclosure.

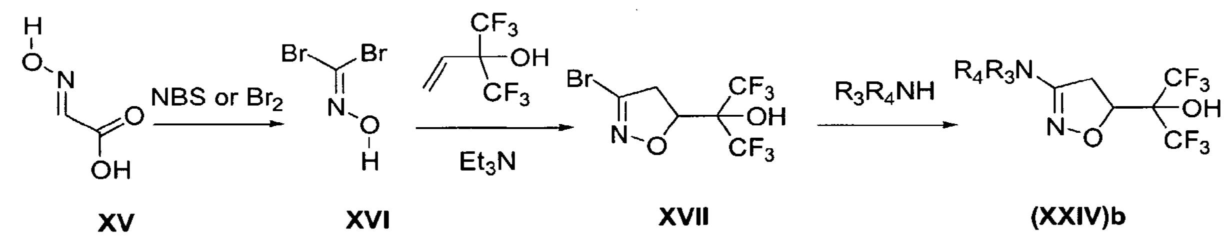
Scheme 1a


CF3
OH
R
G
N
DR4
III
V
IV
G=N or C
D=N or O
HO
F3C
R2
(VIII)
(VII)
VI
X
IX
D=N or O
1, NH2DR4
2. NBS or NCS
3. Base
O
H

Scheme 1b



when R=-COOH



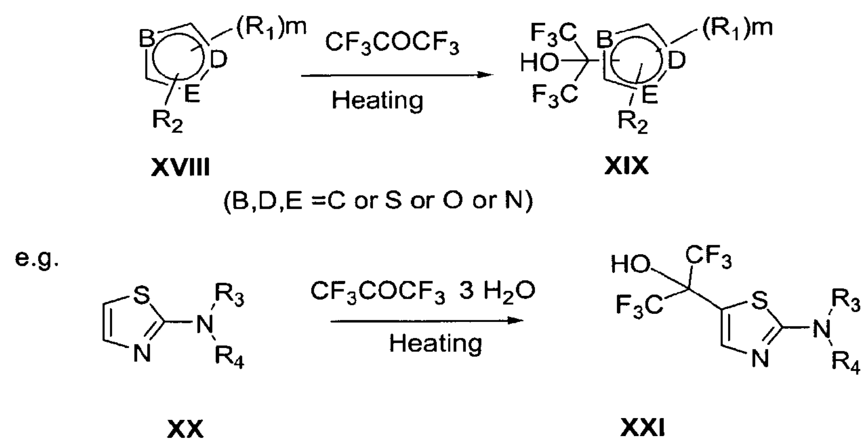
As shown in Scheme 1a, the 1,3-dipolar cycloaddition of dipoles (III) with 1,1,1-trifluoro-2-trifluoromethyl-but-3-yn-2-ol or 1,1,1-trifluoro-2-trifluoromethyl-but-2-en-2-ol can afford relevant hexafluoroisopropanol derivatives of five membered heterocycles (IV) or (V).

Alternatively hexafluoroisopropanol derivatives of five membered heterocycles (IX) or (X) can be synthesized from the cycloaddition of dipoles containing hexafluoroisopropanol (VI) with alkynes (VII) or alkenes (VIII).

For example (Scheme 1b), cycloaddition of nitrile oxides (XII) with 1,1,1-trifluoro-2-trifluoromethyl-but-3-yn-2-ol or 1,1,1-trifluoro-2-trifluoromethyl-but-2-en-2-ol provides respectively the hexafluoroisopropanol derivatives of isoxazole (XIII) or isoxazoline (XIV). The nitrile oxide (XII) can be formed in situ from an aldoxime (XI), which is prepared from the condensation of aldehyde with

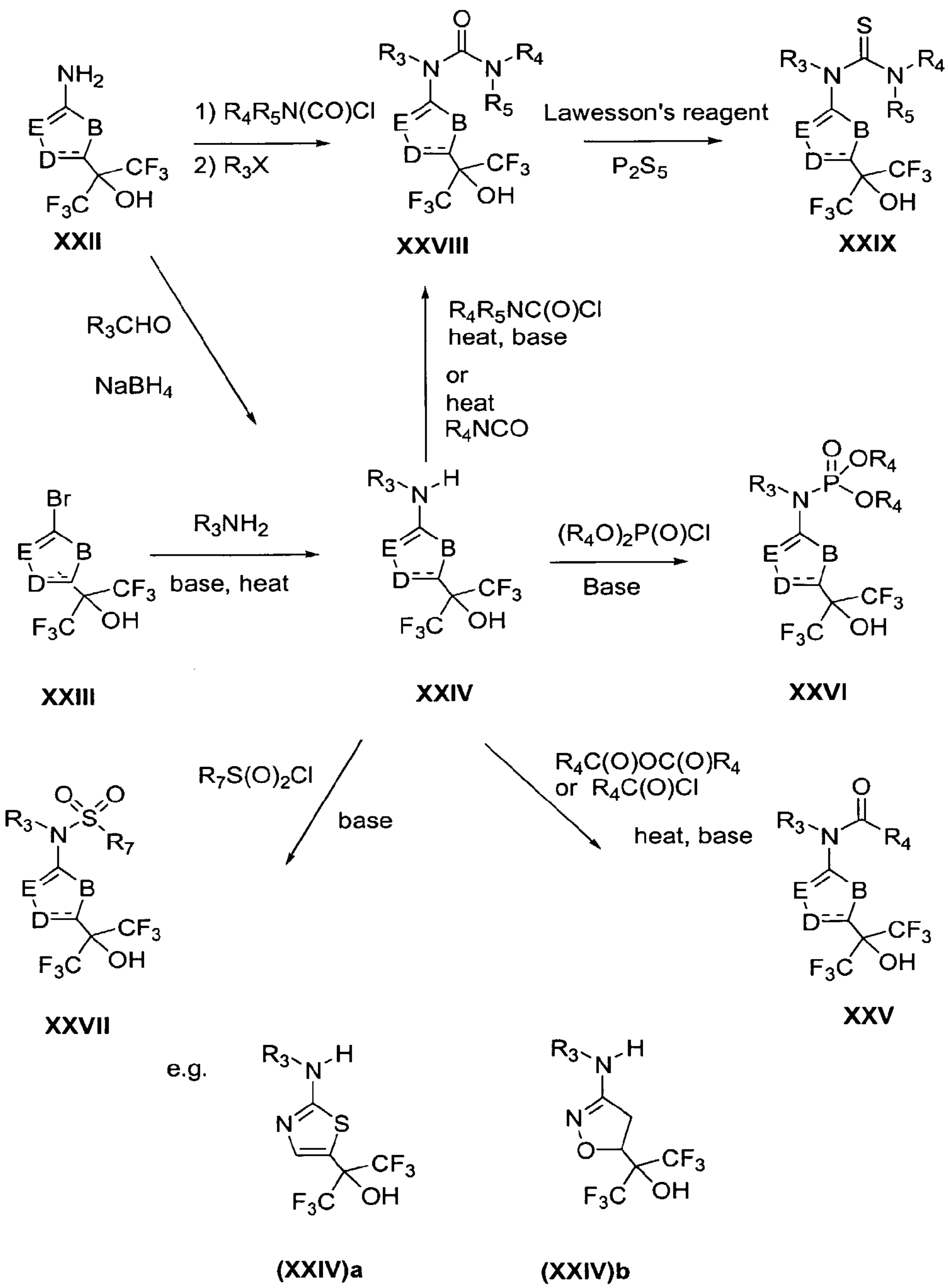
hydroxyamine, by treatment with a chlorinating or brominating agent and a weak base. However bromination of hydroxyimino-acetic acid (XV) affords hydroxy-carbonimidic acid dibromide (XVI) which reacts with (II) to provide 2- (3-bromo-4,5-dihydro-isoxazol-5yl)-1,1,1,3,3,3-hexafluoro-propan-2-ol (XVII). Reaction of (XVII) with alkylamines gives rise to corresponding alkylaminoderivatives (XXIV)b.

Scheme 2



Scheme 2 describes a method for preparation of hexafluoroisopropanol derivatives (XIX) by reacting aromatic heterocycles (XVIII) with hexafluoroacetone. For instance, reaction of 2-alkylamino-1, 3-thiazoles or amino-1,3-thiazoles (XX) with hexafluoroacetone hydrate under heating conditions yields the hexafluoroisopropanol derivatives of 1, 3-thiazole (XXI).

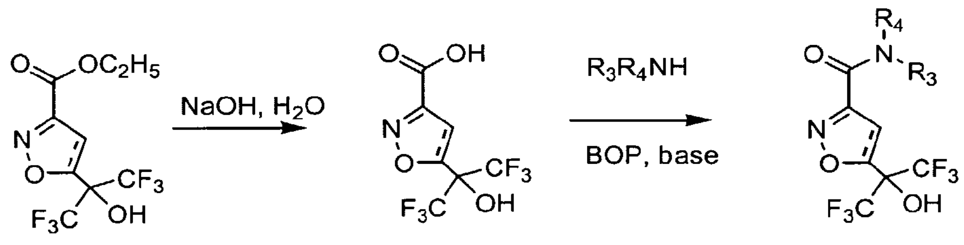
Scheme 3



Hexafluoroisopropanol derivatives of five membered aromatic or non aromatic heterocyclic rings (XXIV), for example 2-N-alkylthiazolyl-hexafluoroisopropanol (XXIV)a, or 1,1,1,3,3,3-Hexafluoro-2-(3-alkylamino-4,5-dihydro-isoxazol-5yl)-propan-2-ol (XXIV)b, are converted into the corresponding

amides (XXV), amidophsphates (XXVI), sulfonamides (XXVII), ureas (XXVIII), carbamates (XXV, R_4=OR_3) and thioureas (XXIX) under reaction conditions depicted in Scheme 3.

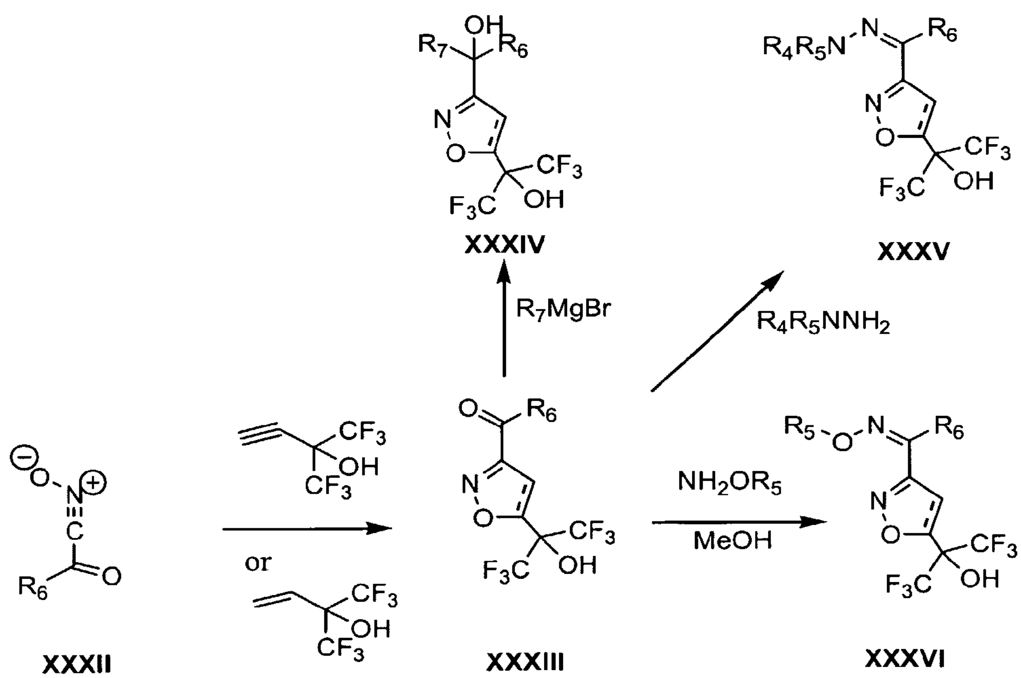
Scheme 4



XXX XXXI

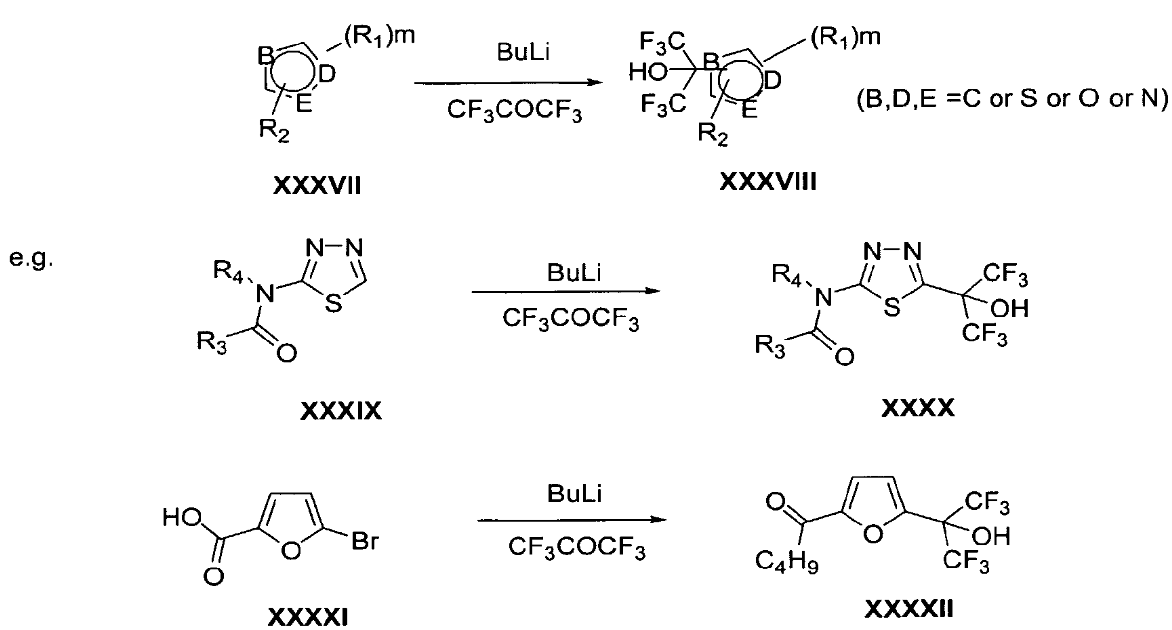
As shown in scheme 4, amide derivatives of isoxazoline or isoxazole (XXXI) are prepared from the coupling of acid derivatives (XXX) with amines in the presence of a coupling reagent such as (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate (Bop) and a base.

Scheme 5



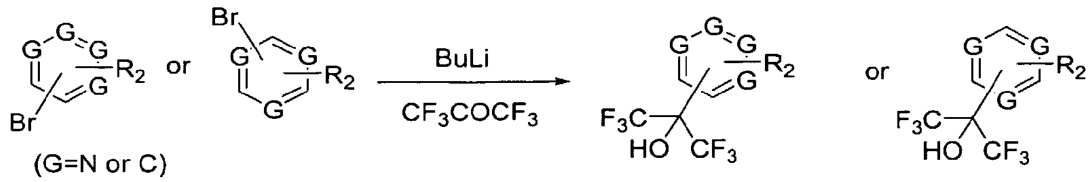
As shown in scheme 5, under depicted reaction conditions, alcohol (XXXIV), hydrazone (XXXV), and oxime (XXXVI) derivatives of isoxazoline or isoxazole can be prepared *via* a common ketone/aldehyde intermediate (XXXIII), which is prepared from 1,3-dipolar reaction of the relevant nitrile oxide (XXXII) with 1,1,1-trifluoro-2-trifluoromethyl-but-3-yn-2-ol or 1,1,1-trifluoro-2-trifluoromethyl-but-2-en-2-ol.

Scheme 6

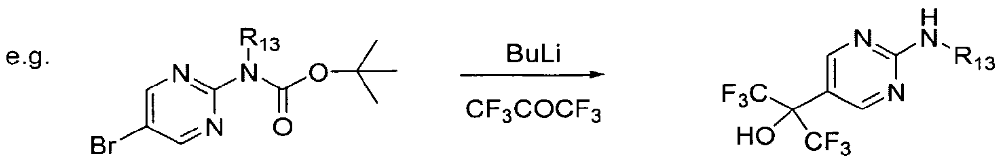


In Scheme 6 an alternative approach to the hexafluoroisopropanol derivatives (XXXVIII) of five membered aromatic heterocyclic rings involves the reaction of hexafluoroacetone with organometallic compounds, which can be formed from (XXXVII). Thus lithiation of intermediates (XXXIX), which are prepared by the reaction of commercially available 2-alkylamino-thiadiazole with acid chlorides, followed by the addition of hexafluoroacetone, gives the desired hexafluoroisopropanol derivatives (XXXX). On the other hand, reaction of 5-bromo-2-furoic acid (XXXXI) with excess amount of n-butyl lithium followed by the treatment with hexafluoroacetone provides 1-{5-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl) ethyl] furan-2-yl} pentan-1-one (XXXXII).

Scheme 7



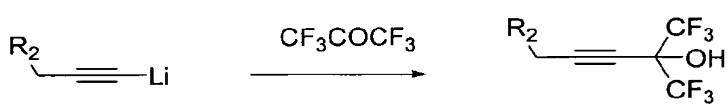
XXXXIII XXXXIV



XXXXV XXXXVI

The hexafluoroisopropanol derivatives (XXXXIV) of six membered heterocyclic rings containing one to four nitrogen atoms can be prepared by the method presented in Scheme 7. Thus treatment of 5-bromo-2-aminopyrimidine derivative (XXXXV) with n-butyllithium results in halogen-lithium exchange and subsequent reaction of the corresponding lithium intermediate with hexafluoroacetone affords hexafluoroisopropanol pyrimidine derivative (XXXXVI).

Scheme 8



XXXXI XXXXII

Scheme 8 depicts the method of synthesis of alkynyl hexafluoroisopropanol derivatives. For example, reaction of hexafluoroacetone with alkynyl lithiums (XXXXVII), prepared by the treatment of alkynes with n-butyl lithium, gives rise to alkynyl hexafluoroisopropanol derivatives (XXXXVIII).

BIOLOGICAL ACTIVITY

***In Vitro* LXRα and β activity assay:**

The assays for gene expression (apoE, ABCA1, and SREBP-1c) are performed following the literature procedures (Sparrow et al., *J. Biol. Chem.* **277**:10021-10027(2002); Laffitte et al., *Proc. Natl. Acad. Sci.,* **98**:507-512(2001); Repa et al., *Genes Dev.* **14**:2819-2830(2000)). LXR modulator refers to compounds which achieve at least 50% activation or inhibition of LXR relative to 24(S)25-epoxycholesterol, the positive control, or which stimulate the expression of the responsive genes, such as ABCA1 genes, in a cell system.

To determine the effectiveness of representative compounds of the present invention as LXR modulators, THP-1 cells were maintained in suspension for passage and growth in PRMI 1640 (Invitrogen) containing 10% FBS (Irvine Scientific, Santa Ana, CA), 100 units/ml penicillin/100ug/ml streptomycin (Irvine Scientific), 1mM sodium pyruvate (Invitrogen) and 55 uM β-mercaptoethanol (Sigma). Passaging was performed every 3-4 days at a 1:4 dilution. For experiments, 1X106 cells/well were plated in 6-well plates in media supplemented with 100 ng/ml phorbol 12-myristate-13-acetate (PMA, Sigma) to induce differentiation. Cells were maintained in this media for 5-days prior to treatment with LXR agonists. Generally, the culture media was replaced with media containing vehicle (DMSO or ethanol) or 1-10 uM drugs at 0 h. THP-1 cells were dosed a second time at 24 h and then harvested for RNA isolation 24 h later.

Total RNA samples were diluted to 100 ug/ml and treated with 40 units/ml RNA-free Dnase I (Ambion, Austin, TX) for 30 min at 37^{o}C followed by inactivation at 75oC for 5 min. Samples were quantitated by spectrophotometry or with the RiboGreen assay (Molecular Probes, Eugee, OR) and diluted to a concentration of 10ng/ul. Samples were assayed in duplicate 25-ul reactions using 35ng of RNA/reaction with PerkinElmer chemistry on an ABI Prism 7700 (Applied Biosystems). Gene specific primers were used at 7.5 or 22.5 pmol/reaction and optimized for each gene examined, and the gene-specific fluorescently tagged probe was used at 5 pmol/reaction. In this system, the probe is degraded by Taq polymerase during the amplification phase, releasing the fluorescent tag from its quenched state; amplification data is expressed as

the number of PCR cycles required to elevate the fluorescence signal beyond a threshold intensity level. Fold induction values were calculated by subtracting the mean threshold cycle number for each treatment group from the mean threshold cycle number of the vehicle group and raising 2 to the power of this difference.

As shown in Table A, LXR modulating activity was determined from the magnitude of gene expression induction as compared to a control (DMSO). Compounds showing significant induction of the ABCA1 gene in a THP-1 cell system, as compared to the control (DMSO), demonstrates that the compounds of the present invention are useful LXR modulators for increasing ABCA1 expression, increasing HDL cholesterol and treating LXR mediated diseases or conditions such as hypercholesterolemia and cardiovascular diseases.

Table A. Gene Expression Induction

Compound Example	**ABCA1 Gene Fold of Induction**		
	100 nM	**1 uM**	**10 uM**
Example 8-3-6	1.37	1.42	1.38
Example 1-2-1	1.58	1.83	2.49
Example 8-3-17	1.56	1.66	1.79

EXAMPLES

To further illustrate this invention, the following examples are included. The examples should not, of course, be construed as specifically limiting the invention. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the invention as described, and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples.

Trademarks used herein are examples only and reflect illustrative materials used at the time of the invention. The skilled artisan will recognize that variations in lot, manufacturing processes, and the like, are expected. Hence the examples, and the trademarks used in them are non-limiting, and they are not intended to be limiting, but are merely an illustration of how a skilled artisan may choose to perform one or more of the embodiments of the invention.

^1H nuclear magnetic resonance spectra (NMR) is measured in $CDCl_3$ or other indicated solvents on a Varian NMR spectrometer (Unity Plus 400, 400 MHz for ^1H) unless otherwise indicated and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak multiplicities are denoted as follows, s, singlet; d, doublet; t, triplet; m, multiplet.

The following abbreviations have the indicated meanings:

Bn = benzyl

DMAP = 4-(dimethylamino)-pyridine

DMF= N,N-dimethylformamide

DMSO = dimethylsulfoxide

ESIMS = electron spray mass spectrometry

Et_3N = triethylamine

EtOAc = ethyl acetate

Lawesson's reagent = 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide

$MgSO_4$ = magnesium sulfate

$NaHCO_3$ = sodium bicarbonate

NBS = N-bromosuccinimide

NCS = N-chlorosuccinimide

NH_4Cl= ammonium chloride

Ph = phenyl

Py = pyridyl

r.t.= room temperature

THF = tetrahydrofuran

TLC = thin layer chromatography

Alkyl group abbreviations

Me = methyl

Et = ethyl

n-Pr = normal propyl

i-Pr = isopropyl

c-Pr =cyclopropyl

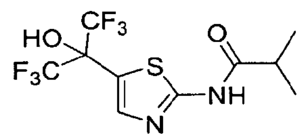
n-Bu = normal butyl

i-Bu = isobutyl

t-Bu = tertiary butyl
s-Bu = secondary butyl
c-Hex = cyclohexyl

Example 1-1-1

Preparation of 2-methyl-N- {5-[2,2,2-trifluoro-1-hydroxy-1- (trifluoromethyl) ethyl]-1,3-thiazol-2-yl} propanamide



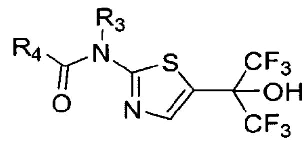
Step 1
Preparation of 2-(2-amino-1, 3-thiazol-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol

A catalytic amount of molecular sieves powder (4A) was added to a mixture of 2-aminothiazole 200 mg (2 mmol) and hexafluoroacetone trihydrate (880 mg, 4 mmol). The mixture was heated at 100 °C for 8 h. Ethyl acetate was added and the mixture was filtered. Organic solvents were evaporated under reduced pressure. The residue was recrystallized in THF and hexanes to afford the title product (389 mg) as a white solid. ^{1}H NMR (DMSO-d6) δ7.12 (s, 1H), 7.45 (brs, 2H), 8.85(s, 1H); ESIMS: *m/z* 267 (M+H).

Step 2

To a solution of 2-(2-amino-1, 3-thiazol-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (267 mg, 1 mmol) obtained above in triethylamine (150 mg, 1.49 mmol) and THF (10 ml), was added isobutyryl chloride (110 mg 1.03 mmol) at room temperature. The reaction mixture was stirred for 30 minutes. Solvent was removed under reduced pressure and the residue was dissolved in EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was recrystallized in THF and hexanes to afford the title compound (282 mg) as a white solid. ^{1}H NMR (DMSO-d6) δ1.08 (d, 6H), 2.72 (m, 1H), 7.60 (s, 1H), 9.10 (brs, 1H), 12.3 (brs, 1H); ESIMS: 319 (M-OH).

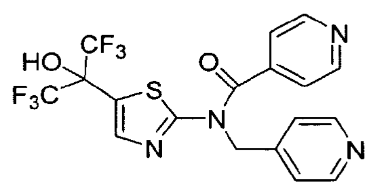
Table 2. The following compounds are prepared in accordance with the procedure described in the example 1-1-1.



Example	R_3	R_4
Example 1-1-1	H	i-Pr-
Example 1-1-2	H	$PhCH_2CH_2$-
Example 1-1-3	H	Ph-

Example 1-2-1

Preparation of N-(pyridin-4-ylmethyl)-N-{5-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-1,3-thiazol-2-yl}pyridine-4-carboxamide



Step 1

Preparation of 1,1,1,3,3,3-hexafluoro-2- {2-[(pyridin-4-ylmethyl) amino]-1,3-thiazol-5-yl} propan-2-ol

A mixture of 2-aminothiazole (3 g, 30 mmol) and 4-pyridinecarboxaldehyde (3.21 g, 30 mmol) in toluene (50 ml) was refluxed with a Dean-Stark water separator for 3 h. Solvent was removed under reduced pressure and the resulting yellow solid was dissolved in CH_3OH (80 ml). The solution was carefully treated with sodium borohydride (1.8 g) and was stirred for 20 minutes. The reaction mixture was quenched with 1N NaOH and evaporated to dryness. The residue was dissolved in EtOAc , washed with brine and dried ($MgSO_4$). Solvent was evaporated to give the crude intermediate N-(pyridin-4ylmethyl)-1,3-thiazol-2-amine as a brown solid (4.2 g).

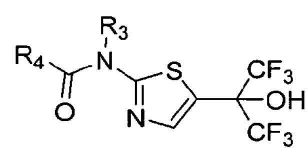
Molecular sieves powder (4A) (1 g) was added to a mixture of crude intermediate N- (pyridin-4ylmethyl)-1,3-thiazol-2-amine prepared above (2.5 g 13 mmol) and hexafluoroacetone trihydrate (4 g, 18.1 mmol) in benzene (3ml). The

mixture was heated at 80 °C for 24 h. Acetonitrile was added and mixture was filtered. Solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel, eluting with a 95:5 mixture of $CHCl_3$ and CH_3OH, to afford the title compound as an orange solid (1.1 g). ^1H NMR (DMSO-d6) δ 4.3 (d, 2H), 7.10 (s, 1H), 7.42 (d, 2H); 7.78 (d, 2H), 8.45 (brs, 1H), 8.82 (brs, 1H); ESIMS: *m/z* 356 (M-H).

Step 2

To a solution of 1,1,3,3,3-hexafluoro-2- {2-[(pyridin-4-1yl-methyl) amino]-1,3-thiazol-5-yl} propan-2-ol (714.5 mg, 2 mmol) obtained from step 1 in dioxane (8 ml) was added isonicotinic anhydride (912 mg, 4 mmol). The reaction mixture was refluxed at 100 °C for 2 h and then concentrated under reduced pressure. The residue was extracted with EtOAc (3 X 100ml). The organic layer was washed with H_2O (3 X 40 ml) and dried over $MgSO_4$. Solvent was evaporated to give a residue which was purified by recrystallization from ethyl acetate and hexanes to afford the title compound as a light yellow solid (528 mg). (DMSO-d6) δ5.28(s, 2H), 7.12 (d, 2H), 7.49 (d, 2H), 7.72 (s, 1H), 8.42 (d, 2H) 8.65 (d, 2H); 9.3 (brs, 1H); ESIMS: *m/z* 461 (M-H).

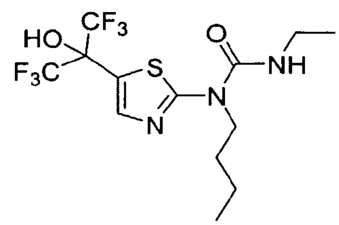
Table 3. The following compounds are prepared in accordance with the procedure described in the above example 1-2-1.



Example	R_3	R_4
Example-1-2-1	4-Py-CH_2-	Py-
Example-1-2-2	n-Bu-	CH_3-
Example-1-2-3	n-Bu-	iPr-
Example-1-2-4	2-Furanyl-CH_2-	i-Pr-
Example-1-2-5	3-Py-CH_2-	iPr-
Example-1-2-6	n-Bu-	4-Py-
Example-1-2-7	4-Py-CH_2-	i-Pr
Example-1-2-8	2-Py-CH_2-	i-Pr-
Example-1-2-9	n-Bu-	n-Pr-
Example-1-2-10	Bn-	i-Pr-
Example-1-2-11	n-Bu-	Ph-
Example-1-2-12	4-Py-CH_2-	CH_3-
Example-1-2-13	Et-	i-Pr-
Example-1-2-14	Et-	CH_3-
Example-1-2-15	4-Cyano-Bn-	CH_3-
Example-1-2-16	4-Cyano-Bn-	-CH(Ph)CH_2CO_2H
Example-1-2-17	4-Cyano-Bn-	i-Pr-
Example-1-2-18	2-(1-Methyl-1H-imidazolyl)-CH_2-	I-Pr-
Example-1-2-19	2-Thiazolyl-CH_2-	i-Pr-
Example-1-2-20	4-MeO(O)C-Bn-	i-Pr-
Example-1-2-21	4-Chloro-Bn-	i-Pr-
Example-1-2-22	4-HO(O)C-Bn-	i-Pr-
Example-1-2-23	3,4-Dichloro-Bn-	I-Pr-
Example-1-2-24	4-(5H-tetrazol-5-yl)-Bn-	i-Pr-
Example-1-2-25	4-Methanesulfonyl-Bn-	i-Pr-
Example-1-2-26	4-(2-Carboxy-vinyl)-Bn-	i-Pr-
Example-1-2-27	4-Methoxy-Bn-	i-Pr-
Example-1-2-28	4-Cyano-Bn-	4-Py-
Example-1-2-29	4-Cyano-Bn-	$-CH_2CH_2C(CH_3)_2CO_2H$
Example-1-2-30	4-MeBn-	i-Pr-
Example-1-2-31	4-Cyano-Bn-	$-CH_2CH_2CO_2H$
Example-1-2-32	4-Cyano-Bn-	$-(CH_2)_3CO_2H$
Example-1-2-33	4-MeO_2C-Bn-	4-Py-
Example-1-2-34	Ph-	i-Pr-
Example-1-2-35	Ph-	4-Py-
Example-1-2-36	$MeOCH_2CH_2$-	i-Pr-
Example-1-2-37	4-HO(O)C-Bn-	3,5-Dichloro-Ph-
Example-1-2-38	4-HO(O)C-Bn-	4-Bromo-Ph-
Example-1-2-39	2-Py-CH_2-	3,5-Dichloro-Ph-
Example-1-2-40	2-Py-CH_2-	4-Bromo-Ph-
Example-1-2-41	4-Cyano-Bn-	-CH(Ph)CH_2CH_2COOH
Example-1-2-42	4-Cyano-Bn-	$-CH_2CH_2$CH(Ph)COOH
Example-1-2-43	4-Cyano-Bn-	$-CH_2C(CH_3)_2CH_2CO_2H$
Example-1-2-44	4-Cyano-Bn-	$-CH_2$ CH(Ph)CO_2H

Example 1-3-1

Preparation of N-butyl-N'-ethyl-N- {5-[2,2,2-trifluoro-1-hydroxy-1- (trifluoromethyl) ethyl]-1,3-thiazol-2-yl} urea



Step 1

Preparation of 2-[2-(butylamino)-1,3-thiazol-5-yl]-1,1,1,3,3,3-hexafluoropropan-2-ol

2-aminothiazole (1 g, 10 mmol) and butyraldehyde (1.44 g, 20 mmol) were mixed in dichloroethane (45 ml) and then treated with sodium triacetoxyborohydride (6 g, 28 mmol) and acetic acid (3.6 g 60 mmol). The reaction mixture was stirred at r.t. under a nitrogen atmosphere overnight. The reaction mixture then was quenched by 1N NaOH and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine and dried over $MgSO_4$. The solvent was evaporated to give 2-butylaminothiazole as a brown residue (1.02 g).

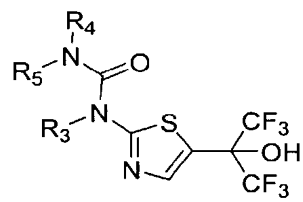
A catalytic amount of molecular sieves powder (4A) was added to the mixture of 2-butylaminothiazole (1 g 6.41 mmol) prepared above and hexafluoroacetone trihydrate (2.86 g 13 mmol). The mixture was heated to gently reflux at 100 °C overnight. EtOAc is added and the mixture was filtered. Solvent was evaporated under reduced pressure. The residue was recrystallized in THF and hexanes to afford the title compound as a white solid. (1.68 g). ^1H NMR δ0.95 (t, 3H), 1.40 (m, 2H), 1.6 (m, 2H), 3.20 (t, 2H), 7.3 (s, 1H); ESIMS: *m/z* 323 (M+H).

Step 2

To a mixture of 2-[2-(butylamino)-1,3-thiazol-5-yl]-1,1,1,3,3,3-hexafluoropropan-2-ol (65 mg, 0.202 mmol) obtained from step 1 in benzene (2 ml) was added ethyl isocyanate (24 µL, 0.3 mmol) under a nitrogen atmosphere The reaction mixture was refluxed for 4 h. Solvent was removed under reduced pressure to obtain an oil, which was dissolved in EtOAc. The resulting solution

was washed with H_2O, saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated to yield a crude product which was purified by preparative TLC (EtOAC:hexanes, 1:3) to afford the corresponding product as a white solid (31 mg). ^1H NMR δ0.92 (t, 3H), 1.20 (t, 3H), 1.37(m, 2H) 1.67 (m, 2H), 3.37 (q, 2H), 3.83 (t, 2H), 4.24 (brs, 1H), 7.50 (s, 1H), 8.60 (brs, 1H); ESIMS: *m/z* 392 (M-H).

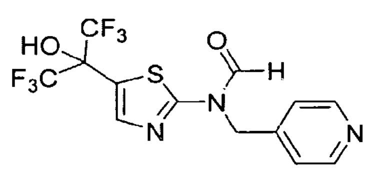
Table 4. The following compounds are prepared in accordance with the procedure described in the above example 1-3-1.



Example	R_3	R_4	R_5
Example 1-3-1	n-Bu-	Et-	H
Example 1-3-2	Et-	c-Hexyl-	H
Example 1-3-3	4-Cyano-Bn-	c-Hexyl-	H
Example 1-3-4	4-Cyano-Bn-	n-Pr-	H
Example 1-3-5	4-Cyano-Bn-	i-Pr-	H
Example 1-3-6	4-Cyano-Bn-	$EtOC(O)CH_2$-	H
Example 1-3-7	n-Bu-	c-Hexyl-	H
Example 1-3-8	Et-	Et-	H
Example 1-3-9	4-Py-CH_2-	Et-	H

<u>Example 1-4</u>

Preparation of pyridin-4-yl methyl {5-[2,2,2-trifluoro-1-hydroxy-1- (trifluoromethyl) ethyl]-1,3-thiazol-2-yl} formamide

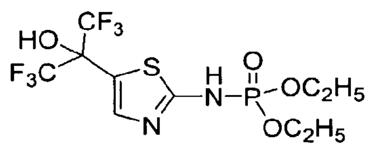


To acetic-formic anhydride (1.5 ml) was added 1,1,3,3,3-hexafluoro-2- {2-[(pyridin-4-1ylmethyl) amino]-1,3-thiazol-5-yl} propan-2-ol (72 mg, 0.201 mmol)

obtained from step 1 of example 1-2-1. The reaction mixture was stirred at r.t. overnight and then concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O, saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Solvent was evaporated to give a residue which was purified by preparative TLC ($CHCl_3$:CH_3OH, 95:5) to afford the title compound as a white solid (38 mg). (DMSO-d6) δ5.28(s, 2H), 7.26 (d, 2H), 7.65 (s, 1H); 8.48 (d, 2H) 8.98 (s, 1H); 9.31 (brs, 1H); ESIMS: *m/z* 384 (M-H)

Example 2

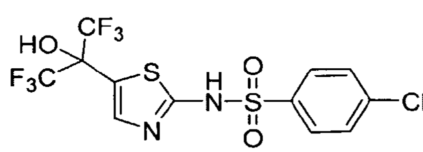
Preparation of diethyl 5-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-1,3-thiazol-2-yl-amidophosphate



To a solution of (2-amino-1, 3-thiazol-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (133mg 0.5 mmol) from step 1 of example 1-1-1, DMAP (61 mg, 0.5 mmol), Et_3N (100 μL, 0.72 mmol) and CH_2Cl_2 (5 ml) was added diethyl chlorophosphate (87 μL, 06 mmol). The reaction mixture was stirred at r.t. for 96 h. Solvent was removed and EtOAc was added. The solution was washed with water. After removal of solvent, the residue was purified by a short Ion Exchange Column (Dowex-50W, ethanol) to afford the title compound as a white solid (43 mg). ^1H NMR (DMSO-d_6) δ 1.20 (t, 6H), 3.89 (m, 4H), 7.46 (s, 1H), 9.18 (s, 1 H); ESIMS: *m/z* 401 (M-H).

Example 3

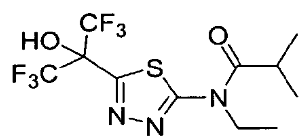
Preparation of 4-chloro-N- {5-[2,2,2,-trifluoro-1-hydroxy-1-(trifluoromethyl) ethyl]-1,3-thiazol-2yl} benzenesulfonamide



To a solution of (2-amino-1, 3-thiazol-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (79.8mg 0.3 mmol) from step 1 of example 1-1-1 in pyridine (1 ml) was added 4-chlorobenzensulfonyl chloride 63.3mg (0.3 mmol). The reaction mixture was stirred at r.t. for 24 h. Pyridine was removed under reduced pressure to yield the residue, which was washed with 1N HCl to give a light brown solid. The solid was washed by water, saturated $NaHCO_3$, brine, and dried by vacuum. Further purification by preparative TLC ($CHCl_3$:CH_3OH, 90:10) afforded the title compound as a white solid (38.2 mg). ^1H NMR (DMSO-d6) δ7.55 (s, 1H), 7.60 (d, 2H), 7.78 (d, 2H), 9.50 (s, 1H), 13.2 (brs, 1H); ESIMS: *m/z* 439 (M-H).

Example 4

Preparation of N-ethyl-2-methyl-N- {5-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl) ethyl]-1,2,4-thiadiazol-3-yl} propanamide



Step 1

To a solution of 2-(ethylamino)-1, 3, 4-thioadiazole (1.29 g, 10 mmol) in pyridine (5 ml) was added isobutyryl chloride (1.06 g, 10 mmol) at 0°C. The reaction mixture was stirred at r.t. overnight. Solvent was removed under reduced pressure and ethyl acetate was added. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was evaporated and the residue was recrystallized in $CHCl_3$ and hexanes to afford the intermediate as an orange solid (1.05 g).

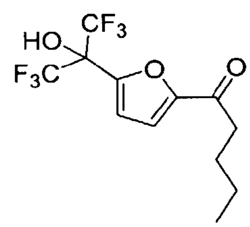
Step 2

To a solution of the intermediate (400 mg 2.0 mmol) prepared above in THF (12 ml) at -78°C, was added n-butyllithium in hexanes solution (2.5 M, 1.2 ml, 3.0 mmol) under a nitrogen atmosphere and the resulting solution was stirred at -78 °C for 30 minutes. Hexafluoroacetone (890 mg, 5.36 mmol) was bubbled into this solution and the resulting mixture was stirred at -78 °C for another 30 minutes. The reaction mixture was quenched with H_2O and allowed to warm up. The solvent was removed and ethyl acetate was added. The organic layer was

washed with aqueous NH_4Cl, H_2O, and brine, then dried ($MgSO_4$) and evaporated. Purification by preparative TLC (hexanes:ethyl acetate, 50:50) afforded the title compound as a white solid (186 mg). ^1H NMR (DMSO$_4$-d6) δ1.10(d, 6H), 1.28 (t, 3H), 3.1 (m, 1H), 4.25 (q, 2H), 9.90 (brs, 1H); ESIMS: *m/z* 364 (M-H).

Example 5

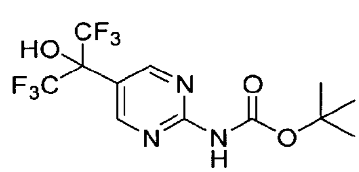
Preparation of 1-{5-[2,2,2-trifluoro-1-hydroxy-1- (trifluoromethyl) ethyl] furan-2-yl} pentan-1-one



To a solution of 5-bromo-2-furoic acid (191 mg 1 mmol) in THF (8 ml), was added n-butyllithium in hexanes solution (2.5 M, 1.2 ml, 3 mmol) at -78°C under a nitrogen atmosphere. The resulting mixture was stirred at -78 °C for 30 minutes. Hexafluoroacetone (1.2 g, 7.3 mmol) was bubbled into the reaction mixture and the resulting solution was stirred for another 30 minutes at -78 °C. The reaction mixture was allowed to warm to r.t. and then quenched with H_2O. Solvent was evaporated, and the residue was dissolved in EtOAc. The organic layer was washed with H_2O and brine, dried ($MgSO_4$) and evaporated. The residue was purified by preparative TLC (hexanes:ethyl acetate, 2:1) to afford the title compound (109 mg) as a yellow oil. ^1H NMR δ0.93 (t, 3H), 1.38 (m, 2H), 1.68 (m, 2H), 2.80 (t, 2H), 7.19 (d, 1H), 7.80 (d, 1H); ESIMS: *m/z* 319 (M+H).

Example 6

Preparation of 1,1-dimethylethyl 5-[2,2,2-trifluoro-1-hydroxy-1- (trifluoromethyl) ethyl] pyrimidin-2-yl-carbamate



Step1

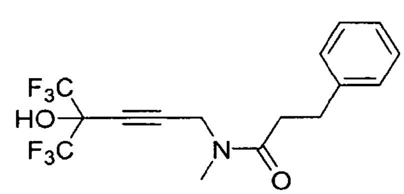
To a mixture of 2-amino-5-bromopyridine (3.48 g 20 mmol), triethylamine 6.1ml (43.7 mmol) and 4-(dimethylamino)-pyridine (244 mg 2 mmol) in THF (60 ml) was added di-t-butyl dicarbonate (9.82 g, 45 mmol). The reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure, and the residue was recrystallized in THF and hexanes. Further purification by flash-chromatography (silica gel, ethyl acetate: haxanes, 1:4) afforded di(t-butyl) 5-bromopyrimidodicarbonate (6.1 g) as a white solid.

Step2

To a solution of intermediate described above (190 mg, 0.51 mmol) in THF (8 ml) at -100 °C, was added n-butyllithium in hexanes solution (2.5 M, 0.8 ml, 2 mmol) under a nitrogen atmosphere, and the resulting reaction mixture was stirred at -100 °C for 30 minutes. Hexafluoroacetone (540 mg, 3.35 mmol) was bubbled into this mixture and the resulting solution was stirred at -100 °C for another 30 minutes. The reaction mixture was quenched with H_2O and allowed to warm to r.t. Solvent was removed and ethyl acetate was added. The organic layer was washed with H_2O and brine, dried ($MgSO_4$) and evaporated. Purification by preparative TLC (hexanes:ethyl acetate, 3:1) afforded the corresponding compound as a white solid (18.6 mg). ^1H NMR ($DMSO_4$-d6) δ1.40 (s, 9H), 8.86 (s, 2H), 9.2 (brs, 1H), 10.40 (brs, 1H); ESIMS: *m/z* 360 (M-H).

Example 7-1

Preparation of N-methyl-3-phenyl-N- [5,5,5-trifluoro-4-hydroxy-4- (trifluoromethyl) pent-2-ynyl] propanamide



Step 1

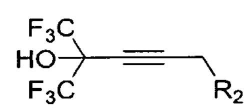
To a solution of N-methylproparglyamine (691 mg, 10 mmol) and triethylamine (1.21 g , 12 mmol) in CH_2Cl_2 (40 ml) was added dropwise a

solution of hydrocinnamoyl chloride (1.68 g 10 mmol) in CH_2Cl_2 (10 ml) at r.t. The reaction mixture was stirred at r.t. for 2 h. Solvent was removed under reduced pressure and the residue was dissolved in EtOAc. The organic layer was washed with water, brine and dried over $MgSO_4$. Concentration afforded the intermediate (1.72 g) as a brown oil, which was further dried by vacuum for several days.

Step2

To a solution of intermediate prepared above (402 mg, 2 mmol) in ether (8 ml) at -78°C, was added n-butyllithium in hexanes solution (2.5 M, 1.2 ml, 3 mmol) under a nitrogen atmosphere. The resulting mixture was stirred at -78 °C for 90 minutes. Hexafluoroacetone (780 mg, 4.7 mmol) was bubbled into the reaction mixture and the resulting solution was stirred for another 30 minutes at -78 °C. The reaction mixture was allowed to warm to r.t. and quenched with H_2O. The mixture was partitioned between ether and water. The organic layer was washed with H_2O and brine, dried ($MgSO_4$) and evaporated. The residue was recrystallized in ether and hexanes to afford the title compound (123 mg) as a white solid. ^{1}H NMR δ2.62 (t, 2H), 2.92 (t, 2H), 2.95 (s, 3H), 4.26 (s, 2H), 7.02-7.30 (m, 5H) ESIMS: *m/z* 366 (M-H).

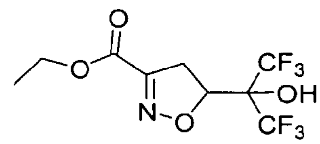
Table 5. The following compounds are prepared in accordance with the procedure described in the example 7-1.



Example 7	R_2
Example 7-1	$PhCH_2CH_2C(O)N(CH_2)$-
Example 7-2	$PhCH_2N(CH_2)$-
Example 7-3	$PhCH_2CH_2C(O)NH$-
Example 7-4	Ph-
Example 7-5	PhS-
Example 7-6	$(n\text{-}Bu)_2N$-

Example 8-1

Preparation of ethyl 5-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-4,5-dihydroisoxazole-3-carboxylate



Step 1

Preparation of 1,1,1-trifluoro-2-trifluoromethyl-but-3-en-2-ol.

To 1.6 M vinylmagnesium chloride in THF (200 mL, 0.32 mol) at -78°C was added hexafluoroacetone (50 g, 0.31 mol) by cannula over a period of 3 h with stirring. The reaction mixture was allowed to warm to r.t. and stirred for an additional 2 h, then heated to 40°C for an additional 1 h. The reaction mixture was quenched with aqueous NH_4Cl solution. The mixture was diluted with pentane, filtered, and the organic phase was dried over $MgSO_4$. Fractional distillation (12 inch Vigreux column) at 100-103°C afforded the product 1,1,1-trifluoro-2-trifluoromethyl-but-3-en-2-ol (mixture containing around 66 mol % THF) as a clear liquid (50 g). ^1H NMR δ 5.20 (br, 1H), 5.70 (d, 1H), 5.92 (m, 2H).

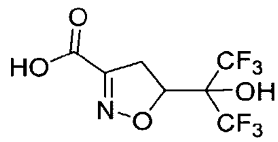
Step 2

Preparation of ethyl 5-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-4,5-dihydroisoxazole-3-carboxylate

To a solution of commercially available ethyl chlorooximidoacetate (3.03 g, 20 mmol) in 1,1,1-trifluoro-2-trifluoromethyl-but-3-en-2-ol (around 90 mmol) from step 1, was added a solution of triethylamine (2.23 g, 22 mmol) in THF (10 mL) by syringe pump over 68 h with stirring at r.t. The reaction mixture was filtered, and the filter cake was washed with ether and pentane. The filtrate was washed with dilute acid and water. Solvents were removed at atmospheric pressure and the residue was purified by column chromatography (EtOAc :Hexanes, 2:1) to afford the ethyl ester (3.06 g, 50%) as a white solid. ^1H NMR δ 1.38 (t, 3H), 3.40 (dd, 1H), 3.60 (dd, 1H), 4.34 (q, 2H), 5.16 (t, 1H).

Example 8-2

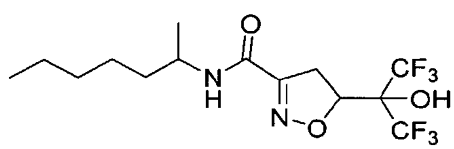
Preparation of 5-[2,2,2-trifluoro-1-hydroxy-1- (trifluoromethyl) ethyl]-4,5-dihydroisoxazole-3-carboxylic acid



To a solution of ethyl 5-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-4,5-dihydroisoxazole-3-carboxylate from example 8-1 (2.58 g, 8.34 mmol) in ethanol (5 ml) was added 1 N NaOH (16.7 mL). The mixture was stirred at r.t. for 1 h. Ethanol was removed under reduced pressure, and to the aqueous solution was added concentrated HCl (1.5 mL). The product was extracted 3 times with EtOAc and 2 times with isopropyl ether, and the combined organic layers were dried over $MgSO_4$. Solvents were removed under reduced pressure to afford the carboxylic acid intermediate as an off-white solid (2.30 g, 98%). ^1H NMR (DMSO-d6) δ 3.2-3.4 (m, 2H), 5.12 (t, 3H), 8.6 (br, 1H); ESIMS: *m/z* 280 (M-H).

Example 8-3-1

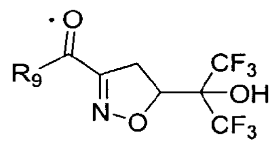
Preparation of N-(1-Methylhexyl)-5-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]-4,5-dihydroisoxazole-3-carboxamide.



A solution of 5-[2,2,2-Trifluoro-1-hydroxy-1- (trifluoromethyl)ethyl)-4,5-dihydroisoxazole-3-carboxylic acid from example 8-2 (84 mg, 0.3 mmol), 2-aminoheptane (69 mg, 0.6 mmol), 4-methylmorpholine (121 mg, 1.2 mmol), and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (265 mg, 0.6 mmol) in DMF (0.5 ml) was stirred at r.t. for 17 h. The reaction mixture was diluted with EtOAc, washed with water, 1 M citric acid and brine, then dried over $MgSO_4$. The solvent was removed under reduced

pressure and the residue was purified by preparative TLC (EtOAc:Haxanes, 2:1) to afford the title compound as a clear oil (74 mg, 65%). ^{1}H NMR δ 0.86 (t, 3H), 1.16 (d, 3H), 1.27-1.45 (m, 8 H), 3.39 (dd, 1H), 3.65 (dd, 1H), 3.99 (m, 1H), 5.11 (t, 1H), 6.36 (d, 1H). ESIMS: *m/z* 377 (M-H).

Table 6. The following compounds are prepared in accordance with the procedure described in the example 8-3.

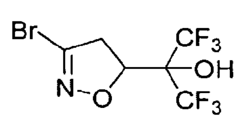


Example	R_9
Example 8-3-1	1-Methyl-hexyl-NH-
Example 8-3-2	Pyrind-4yl-methyl-N(Et)-
Example 8-3-3	$(i\text{-}Pr)_2N$-
Example 8-3-4	$(i\text{-}Bu)_2N$-
Example 8-3-5	$PhCH_2CH_2N(Me)$-
Example 8-3-6	$t\text{-}BuOC(O)CH_2CH_2NH$-
Example 8-3-7	BnNH-
Example 8-3-8	(2-Pyridin-2-yl-ethyl)-N(Me)-
Example 8-3-9	$HOCH_2CH_2N(Et)$-
Example 8-3-10	Et(Ph)N(Me)-
Example 8-3-11	$EtOC(O)CH_2N(Bn)$-
Example 8-3-12	$HO(O)CCH_2CH_2NH$-
Example 8-3-13	$EtOC(O)CH_2CH_2NH$-
Example 8-3-14	1-(2-Et-Piperidinyl)-
Example 8-3-15	1-(2-Me-Pyrrolidinyl)-
Example 8-3-16	bis-(2-Ethyl-hexyl)N-
Example 8-3-17	t-BuOC(O)CH(i-Pr)NH-
Example 8-3-18	$MeOC(O)CH_2CH_2COCH_2NH$-
Example 8-3-19	t-BuOCOCH(Bn)NH-
Example 8-3-20	1-Azepanyl-
Example 8-3-21	1-Piperidinyl-
Example 8-3-22	1-(2-Methyl-aziridinyl)-

Example 8-3-23	(5-t-Butoxycarbonyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-
Example 8-3-24	(Isoamyl) $_2$N-
Example 8-3-25	t-BuOC(O)CH_2CH_2N(i-Bu)-
Example 8-3-26	EtOC(O)CH_2NH-
Example 8-3-27	EtOC(O)$(CH_2)_3$NH-
Example 8-3-28	1-Azetidinyl-
Example 8-3-29	1-Pyrrolidinyl-
Example 8-3-30	1-(2,5-Dimethyl-pyrrolidinyl)-
Example 8-3-3	(2-Oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-
Example 8-3-32	i-BuNH-
Example 8-3-33	c-PrCH_2N(n-Pr)-
Example 8-3-34	2-Ethyl-hexyl-N(pyridin-2-ylmethyl)N-
Example 8-3-35	t-BuCH_2CH_2NH-
Example 8-3-36	EtOC(O)CH_2CH(CO_2Et)NH-
Example 8-3-37	EtOC(O)CH(i-Bu)NH-
Example 8-3-38	t-BuOCO$(CH_2)_2$CH(CO_2Me)NH-
Example 8-3-39	1-(2-CO_2Me)-Piperidinyl-
Example 8-3-40	Pyridin-2-ylmethyl-NH-
Example 8-3-41	Pyridin-3-ylmethyl-NH-
Example 8-3-42	Pyridin-4-ylmethyl-NH-
Example 8-3-43	Pyridin-2-yl-NH-
Example 8-3-44	Pyridin-3-yl-methyl-N(Me)-
Example 8-3-45	$(EtO)_2$C(O)CH(Me)NH-
Example 8-3-46	i-BuN(Me)-
Example 8-3-47	t-BuOC(O)CH(s-Bu)NH-

Example 9-1

Preparation of 2-(3-bromo-4, 5- dihydroisoxazol-5yl)- 1,1,1,3,3,3-hexafluoropropan-2-ol

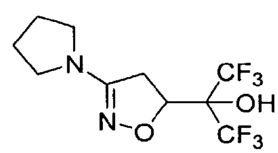


To a solution of glyoxylic acid (1.11 g 15 mmol) in 1.2 ml of H_2O was added a solution of hydroxylamine (0.5 g 15 mmol) in 1ml of water. The solution was

stirred at r.t. for 18 h, then mixed with 10 ml ethylene glycol dimethyl ether. To the stirring solution was added NBS (5.16 g, 29 mmol) over 0.5 h at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for another 0.5 hr. The organic layer was separated and water layer was extracted with ether. The combined and concentrated organic layers (around 10 ml) were added dropwise by syringe pump at r.t. over 4 days to a stirred mixture composed of 1,1,1-trifluoro-2-trifluoromethyl-but-3-en-2-ol (30 mmol, from example 8-1, step 1), potassium bicarbonate (6 g, 60 mmol) and 1 ml water. The reaction mixture was neutralized with 5 N HCl and partitioned between ether and water. The organic layer was separated and washed with brine, dried over $MgSO_4$, and evaporated to dryness. A white solid in 13 % yield was obtained by Kugelrohr distillation (oven temperature, 80-100 °C /15-30 mτ). ^1H NMR (DMSO-d6) δ3.40 (dd, 1H), 3.50 (dd, 1H), 5.20 (t, 1H), 8.70 (s, 1H) ESIMS: *m/z* 315 (M-H).

Example 9-2

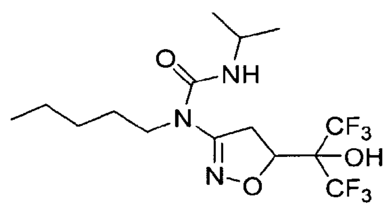
Preparation of 1,1,1,3,3,3-hexafluoro-2-(3-pyrrolidin-1-4,5-dihydroisoxazol-5-yl)propan-2-ol



A mixture of 2-(3-bromo-4, 5- dihydroisoxazol-5yl)- 1,1,1,3,3,3-hexafluoropropan-2-ol (31.6 mg, 0.1 mmol) from example 9-1 and pyrrolidine (28.2 mg, 0.4 mmol) in dioxane (0.5 ml) was heated at 85 °C for 48 h. The mixture was concentrated under reduced pressure and diluted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Solvent was evaporated under reduced pressure, and the residue was recrystalized from CHCl3 and hexanes to afford the title compound as a light brown solid (17.8 mg). ^1H NMR δ 1.94 (m, 4H), 3.10 (dd, 1H), 3.28 (m, 4H), 3.90 (dd, 1H), 4.0 (br, 1H), 4.86 (t, 3H);ESIMS: *m/z* 337 (M+H).

Example 10

Preparation of 3-isopropyl-1-pentyl)-1-[5-(2,2,2-trifluoro-1hydroxy-1-trifluoromethyl-ethyl)-4,5-dihydroisoxazol-3-yl]-urea



Step 1

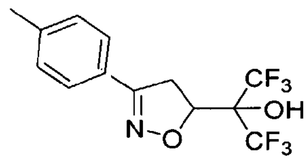
A mixture of 2-(3-bromo-4, 5- dihydroisoxazol-5yl)- 1,1,1,3,3,3-hexafluoropropan-2-ol from example 9-1 (31.6 mg g, 0.1 mmol) and amylamine (26.1 mg, 0.3 mmol) in 0.5 ml of triethylamine was heated at 110 °C in a pressure tube overnight. The reaction mixture was concentrated under vacuum for 5 h to dryness. The residue was directly used as a starting material for next step.

Step 2

To a mixture of the residue from step 1 in 0.5 ml of toluene was added isopropyl isocyanate (30 μL, 0.3 mmol). The reaction mixture was heated at 110 °C in a pressure tube overnight. The organic solvent was removed under reduced pressure and the residue was partitioned between EtOAc and water. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated to dryness. The crude product was purified by preparative TLC (Silica gel, CHCl3:CH3OH, 10:1) to afford the title compound (22.2 mg) as an oil. ^{1}H NMR δ 0.83 (t, 3H), 1.15 (d, 3H), 1.17(d, 3H), 1.30 (m, 4H), 1.57 (m, 2H), 3.25 (d, d, 1H), 3.57 (m, 2H), 3.64 (d, d, 1H), 3.95 (m, 1H), 4.36 (br, 1H), 4.96 (t,1H),7.65 (d, 1H); ESIMS: *m/z* 408 (M+H).

Example 11-1

Preparation of 1,1,1,3,3,3-hexafluoro-2-[3-(4-methylphenyl)-4,5-dihydroisoxazol-5-yl]propan-2-ol



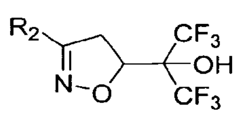
Step 1

To a mixture of p-tolualdehyde (1.2g g 10 mmol)and hydroxylamine hydrochloride(700 mg 10 mmol) in 30 ml ethanol was added soldium methoxide (540 mg, 10 mmol). The reaction mixture was stirred at r.t. for 8 h. The mixture was filtered and evaporated to dryness. The resulting white solid was diluted with 30 ml CH_2Cl_2, to which NCS (1.33 g, 10 mmol) was added. The reaction mixture was stirred at r.t overnight. The mixture was filtered. Solvent was removed and the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate, 3:1) to give a solid in a 44% yield .

Step 2

To a stirred solution of the above compound (170 mg, 1 mmol) in 1,1,1-trifluoro-2-trifluoromethyl-but-3-en-2-ol (2 mmol) was added a solution of triethylamine (121 mg, 1.2 mmol) in THF (10 ml) dropwise by syringe pump at r.t. over 30 h. The mixture was concentrated under reduced pressure and diluted with EtOAc. The organic layer was washed with 1 N HCl, H_2O and dried over $MgSO_4$. Solvent was evaporated under reduced pressure, and the residue was purified by preparative TLC (Hexanes : EtOAc, 5:1) to afford the title compound as a white solid (89.2 mg). ^{1}H NMR δ 2.38 (s, 3H), 3.50 (d,d, 2H), 3.64 (br, 1H), 3.69 (dd, 2H), 5.08 (t, 1H), 7.20 (d, 2H), 7.60 (d, 2 H); ESIMS: *m/z* 342 (M-H).

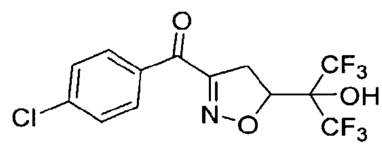
Table 7. The following compounds are prepared in accordance with the procedure described in the example 11-1.



Example	R_2
Example 11-1	p-Tolyl-
Example 11-2	p-CN-Ph-
Example 11-3	5-Methylfuryl-
Example 11-4	p-Bromo-Ph-
Example 11-5	5-(1-Me-2-Cl-pyrrolyl)-

Example 12

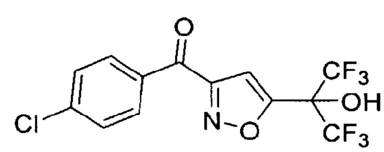
Preparation of (4-Chloro-phenyl)-[5-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)- 4,5-dihydroisoxazol-3-yl]methanone



To a solution of commercially available 4-chlorophenyl glyoxylohydroxamyl chloride (218 mg, 1 mmol) in 1,1,1-trifluoro-2-trifluoromethyl-but-3-en-2-ol (2 mmol) was added a solution of triethylamine (111mg, 1.1 mmol) in THF (10 ml) dropwise by syringe pump at r.t. over 30 h. The mixture was concentrated under reduced pressure and diluted with EtOAc. The organic layer was washed with 1N HCl, H_2O and dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (Hexanes : EtOAc, 4:1) to afford the title compound as a white solid (107.3 mg). ^{1}H NMR δ 3.54 (s, 1H), 3.60 (dd, 1H), 3.76 (dd, 1H), 5.12 (t, 1H), 7.45 (d, 2H), 8.14 (d, 2 H); ESIMS: *m/z* 374 (M-H).

Example 13

Preparation of (4-Chloro-phenyl)-[5-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-isoxazol-3-yl]methanone



Step 1

Preparation of 1,1,1-trifluoro-2-trifluoromethyl-but-3-yn-2-ol

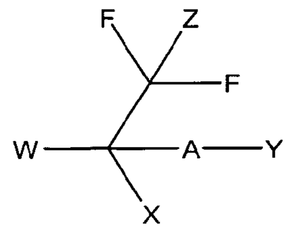
To a 100ml solution of ethynyl magnesium bromide (0.5 M in THF) in an acetone-ethanol dry ice bath was bubbled hexafluoro acetone gas (6.1 g, 36.7 mmol) over 2 h. The reaction mixture was warmed to r.t and then refluxed for 0.5 h. The reaction mixture was quenched with aqueous NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine, and dried over $MgSO_4$. A liquid mixture of 1,1,1-trifluoro-2-trifluoromethyl-but-3-yn-2-ol with THF at b.p. 100-103 °C (4.7 g, contained about 68 mol % THF) was obtained by distillation (12 inch Vigreux column).

Step 2

To a solution of commercially available 4-chlorophenyl glyoxylohydroxamyl chloride (109 mg, 0.5 mmol) in 1,1,1-trifluoro-2-trifluoromethyl-but-3-yn-2-ol from step 1 (about 1 mmol) was added a solution of triethylamine (60 mg, 0.6 mmol) in THF (10 ml) dropwise by syringe pump at r.t. over 30 h. The mixture was concentrated under reduced pressure and diluted with EtOAc. The organic layer was washed with 1N HCl, H_2O and dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (Hexanes: EtOAc, 5:1) to afford the title compound as a white solid (87.2 mg). ^1H NMR (DMSO-d_6) δ 7.37 (s, 1H), 7.60 (d, 2H), 8.14 (d, 2 H), 9.92 (s, 1H); ESIMS: *m/z* 372 (M-H).

We claim:

1. A method for modulating Liver X Receptor (LXR) which comprises the administration of a therapeutically effective amount of a composition selected from the group consisting of compounds of the following formula (I):

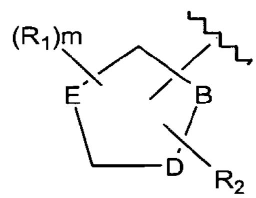


(I)

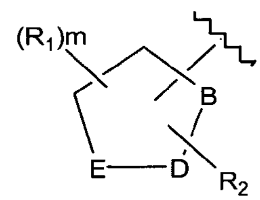
wherein

W is independently chosen from:

a five membered substituted non-aromatic heterocyclic ring containing one double bond having the following formulae (I a) and (I b):



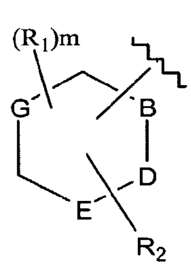
I a



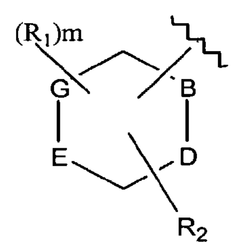
I b

wherein B, D and E represent atoms selected from C, N, O or S;

a six membered substituted non-aromatic heterocyclic ring containing zero to two double bonds having the following formulae (I c) and (I d):



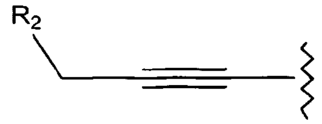
I c



I d

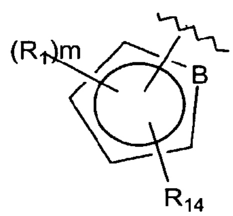
wherein B, D , E and G represent atoms selected from C, N, O or S;

an alkynyl group having the following formula (I e):

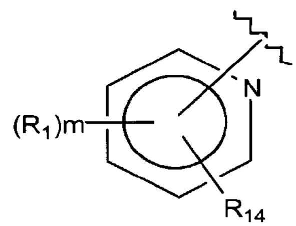


I e

a five or six membered substituted aromatic heterocyclic ring having one heteroatom of the following formulae (II a) and (II b):

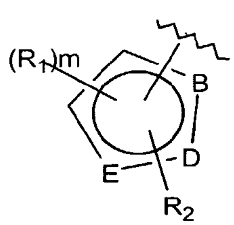


II a

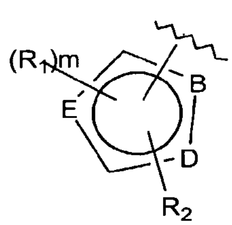


II b

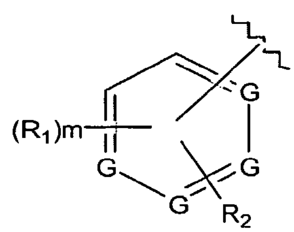
a five or six membered substituted aromatic heterocyclic ring having at least two heteroatoms of the formulae (II c) ,(II d), (II e) and (II f) with the proviso that (II c) and (II d) do not include the pyrazole ring:



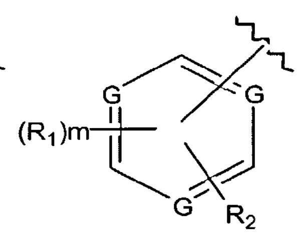
II c



II d



II e



II f

wherein D , E and B represent atoms selected from C, N, O or S, and G represents atoms selected from C or N ;

R_1 is independently chosen from halo, haloalkyl, hydroxy, thiol, substituted thiol, sulfonyl, sulfinyl, nitro, cyano, amino, substituted amino, C_1-C_6 alkyl and C_1-

C_6 alkoxy, and when R_1 is hydroxy, C_1-C_6 alkoxy, thiol, substituted thiol, amino, substituted amino, or C_1-C_6 alkyl, such radical may be combined with R_2 or R_{14} to form a ring of 5-7 members when R_1 is positioned next to R_2 or R_{14};

R_2 is selected from $-N(R_3)C(O)R_4$, $-C(O)NR_4R_5$, $-N(R_3)C(O)NR_4R_5$, $N(R_3)SO_2R_7$, $-N(R_3)SO_2NR_4R_3$, $-N(R_3)C(O)OR_4$, $-C(O)OR_4$, $-C(S)OR_4$, $-SR_3$, Phenyl, $-N(R_3)C(S)NR_4R_5$, $-NR_3R_4$, $-N(R_3)C(=NR_3)NR_4R_5$, $-N(R_3)C(=NCN)NR_4R_5$, $-N(R_3)C(=CHNO_2)NR_4R_5$, $-NR_3P(O)R_4R_5$, $-NR_3P(O)(OR_4)(OR_5)$, $-NR_3P(O)(OR_4)(NR_5)$, $-N(R_3)P(O)(NR_4)(NR_5)$, $-N(R_3)C(=NR_3)R_6$, $-COR_6$, $-C(R_6)(OH)R_7$, $-C(R_8)=NOR_4$, $-C(R_8)=NR_3$, $-C(R_8)=NNR_4R_5$, $-SOR_7$, $-SO_2R_7$, $-P(O)(OR_4)(OR_5)$, $-P(O)(R_4)(R_5)$, $-P(O)(OR_4)(OR_5)$ $-P(O)(NR_3)(OR_4)$, $-P(O)(NR_4)(NR_5)$, a 3-7 membered ring containing from zero to three heteroatoms selected from O, N, or S, which may be substituted by R_9, R_{10}, R_{11}, R_{12} or R_{13}, or may be combined with R_1 to form a ring of 5-7 members when R_1 is positioned next to R_2;

R_3 is hydrogen, alkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, acyl, or may form a ring of 5-7 members with R_4 or R_5;

R_4 is hydrogen, alkyl, aryl, heterocyclyl, acyl, or may form a ring of 5-7 members with R_5 or R_3;

R_5 is hydrogen, alkyl, aryl, or heterocyclyl, acyl or may form a ring of 5-7 members with R_3 or R_4;

R_6 and R_7 may be equal or different and are selected from hydrogen, alkyl, aryl, or heterocylcyl;

R_8 is hydrogen, alkyl, aryl, heterocylcyl, amino or substituted amino;

R_9, R_{10}, R_{11} and R_{12} may be equal or different and are selected from hydrogen, alkyl, aryl, heterocyclyl, nitro, cyano, carboxylic acid, ester, amides, halo, hydroxyl, amino, substituted amino, alkoxy, acyl, ureido, sulfonamido, sulfamido, sulfonyl, sulfinyl, or guanadinyl;

R_{13} is hydrogen, alkyl, aryl, ester, heterocyclyl, acyl, sulfonyl, ureido, or guanadinyl;

R_{14} is selected from $-NR_3C(S)NR_4R_5$, $-NR_3C(=NR_3)NR_4R_5$, $-NR_3C(=NCN)NR_4R_5$, $-NR_3C(=CHNO_2)NR_4R_5$, $-NR_3P(O)R_4R_5$, $-NR_3P(O)(OR_4)(OR_5)$, $-NR_3P(O)(OR_4)(NR_5)$, $-NR_3P(O)(NR_4)(NR_5)$, $-NR_3C(=NR_3)R_6$, $-COR_6$,

$-C(R_6)(OH)R_7$, $-C(R_8)=NOR_4$, $-C(R_8)=NR_3$, $-C(R_8)=NNR_4R_5$, SOR_7, $-SO_2R_7$, $-P(O)(OR_4)(OR_5)$, $-P(O)(R_4)(R_5)$, $-P(O)(OR_4)(OR_5)$, $-P(O)(NR_3)(OR_4)$, $-P(O)(NR_4)(NR_5)$, a 3-7 membered ring containing from zero to three heteroatoms selected from O, N, or S, which may be substituted by R_9, R_{10}, R_{11}, R_{12} or R_{13}, or may be combined with R_1 to form a ring of 5-7 members when R_1 is positioned next to R_{14};

A is O, S, or NR_3;

m is from zero to three;

X is H, CF_2Z, or CF_3, or together with Y forms a double bond when A is O;

Y is hydrogen, or together with X forms a double bond when A is O;

Z is F, Br, Cl, I or CF_3;

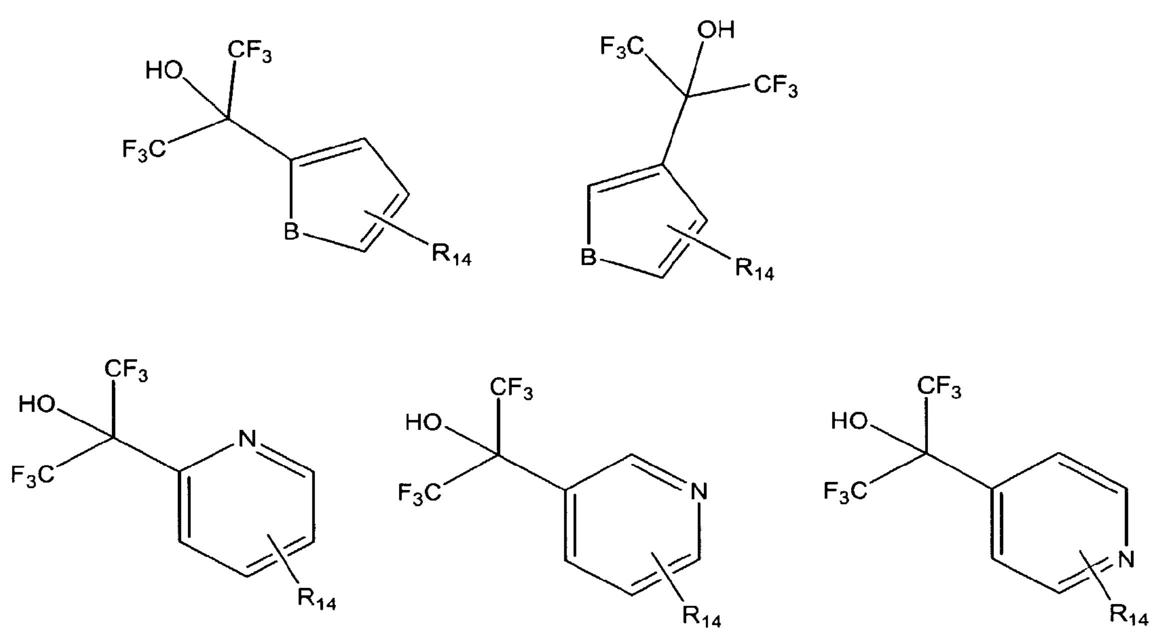
the corresponding enantiomers, diastereoisomers or tautomers,

or a pharmaceutically acceptable salt, or a prodrug thereof in a pharmaceutically-acceptable carrier.

2 A method according to Claim 1 wherein X is CF_3; Y is hydrogen; and Z is F.

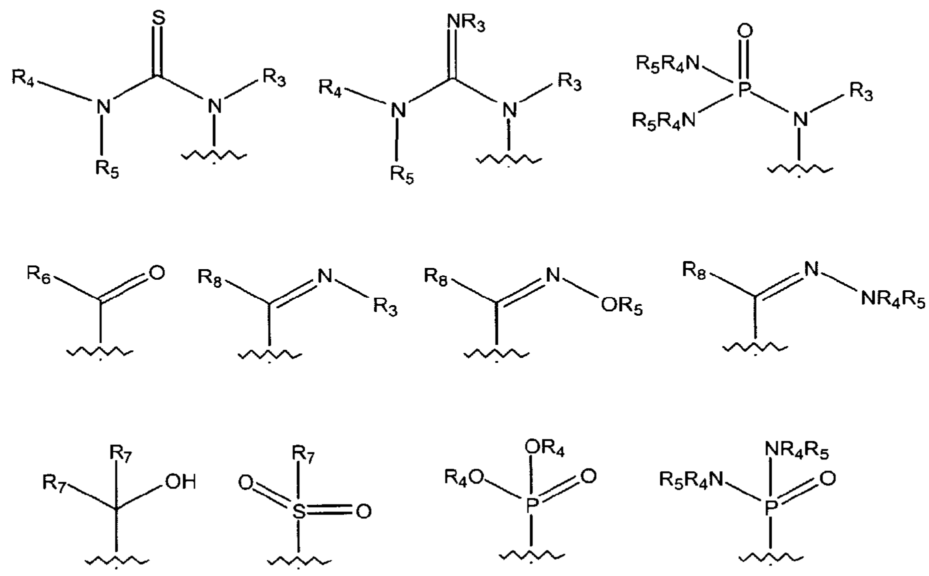
3 A method according to Claim 2 wherein R_1 is hydrogen.

4 A method according to Claim 3 wherein W is a five or a six membered substituted aromatic heterocyclic ring containing one heteroatom and having the following formulae:



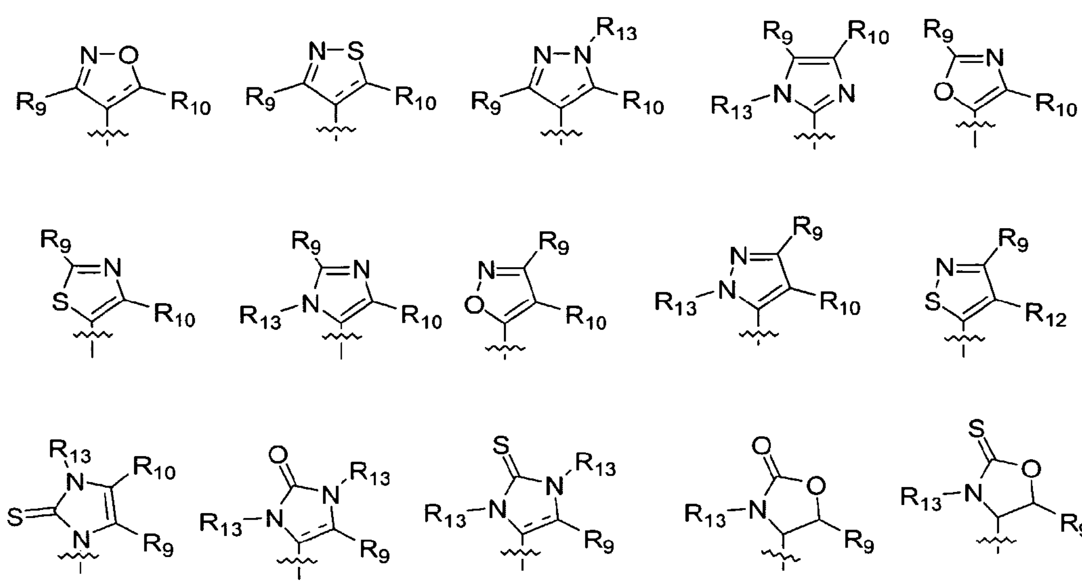
wherein B is selected from N, O or S and R_{14} is as defined above.

5. A method according to Claim 4 wherein R_{14} is selected from the following groups:



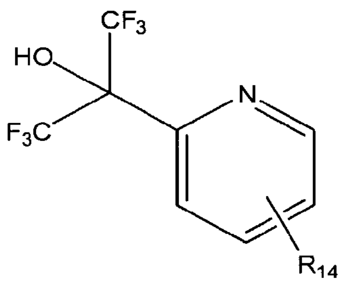
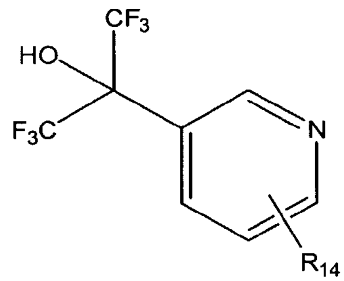
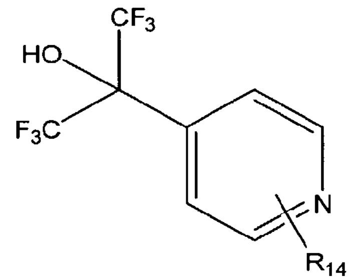
wherein R_3, R_4, R_5, R_6, R_7, and R_8 are defined as above.

6. A method according to Claim 4 wherein R_{14} is selected from a five membered heterocyclic ring containing two to three heteroatoms selected from the following:

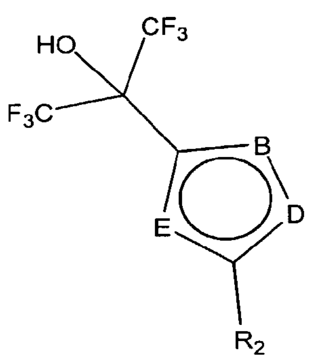
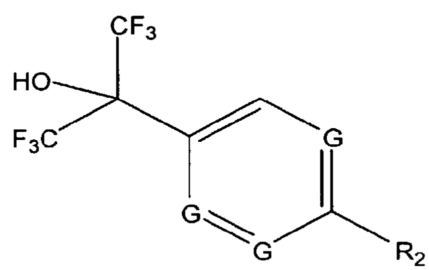
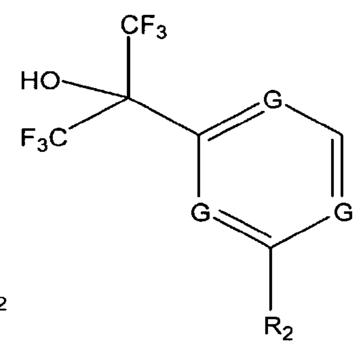


wherein R_9, R_{10}, R_{11}, R_{12} and R_{13} are as defined above.

7. A method according to Claims 5 and 6 wherein W is selected from pyridyl:

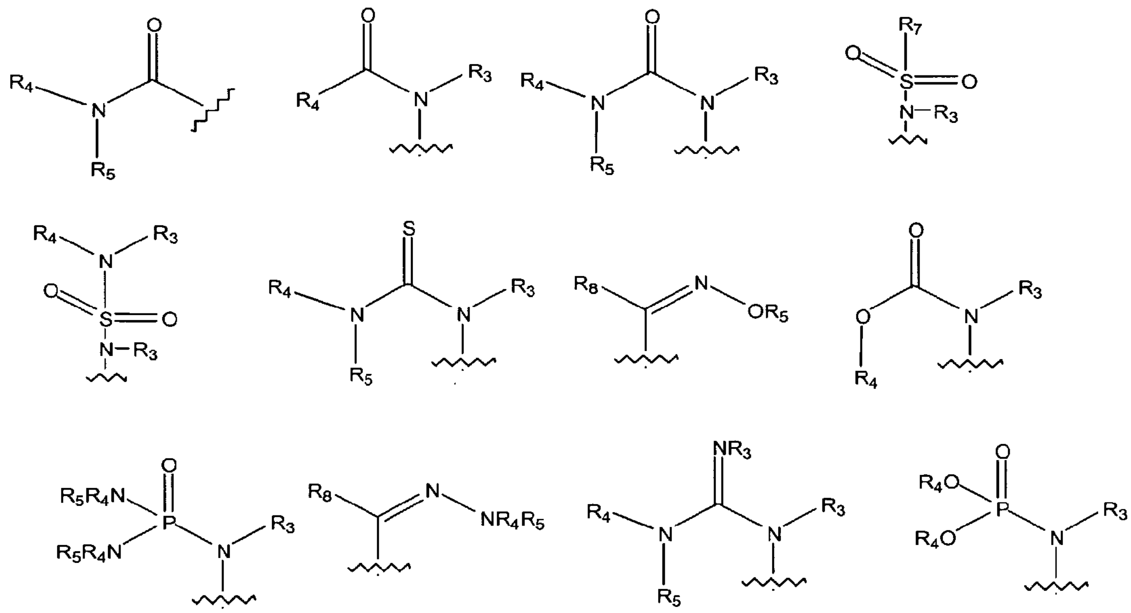




8. A method according to Claim 3 wherein W is a five or six membered substituted aromatic heterocyclic ring containing at least two heteroatoms with the proviso that the pyrazole ring is not included and having the following formulae:

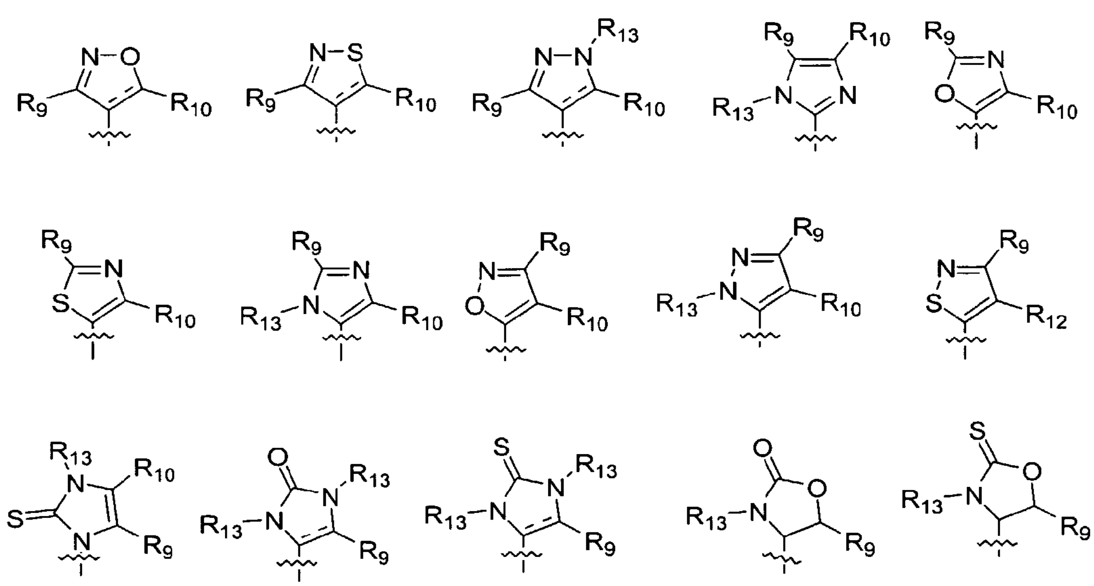
wherein R_2 is as defined as above and D , E and B represent atoms selected from C, N, O or S, and G represents atoms selected from C or N.

9. A method according to Claim 8 wherein R_2 is chosen from the following groups:



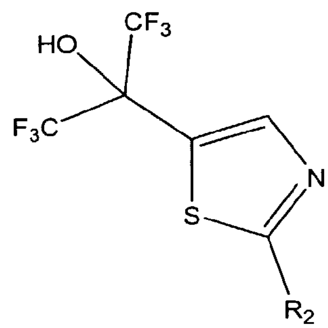
wherein R_3, R_4, R_5, R_6, R_7, and R_8 are defined as above.

10. A method according to Claim 8 wherein R_2 is selected from the following groups:

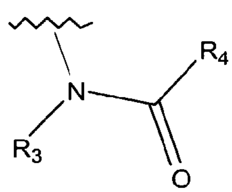


wherein R_9, R_{10}, R_{11}, R_{12} and R_{13} are as defined above.

11. A method according to Claim 8 wherein said five membered aromatic heterocyclic ring is of the formula:

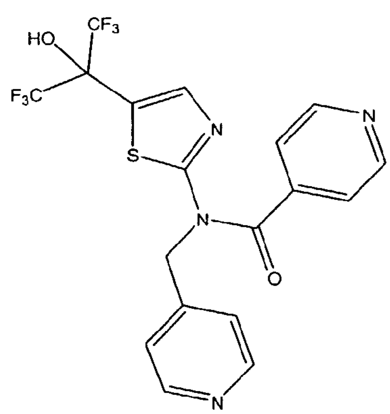


12. A method according to Claim 11 wherein R_2 has the following formula:

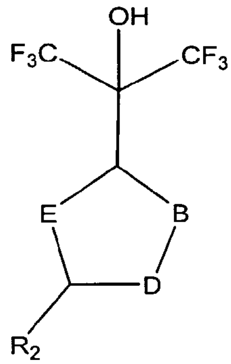


13. A method according to Claim 12 wherein R_4 is a substituted aryl and R_3 is a substituted arylalkyl.

14. A method according to Claim 13 having the formula:

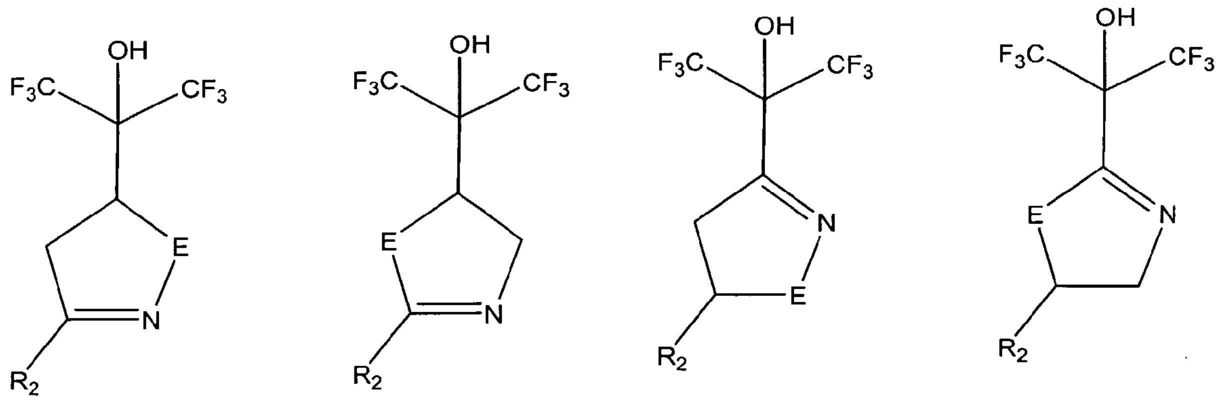


15. A method according to Claim 3, wherein W is chosen from a five membered substituted non-aromatic heterocyclic ring containing one double bond and having the following formula:



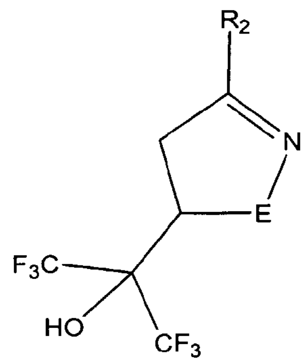
wherein at least one of B, D and E represents a heteroatom selected from O, S or N.

16. A method according to Claim 15 wherein said five membered substituted non-aromatic heterocyclic ring is of the following formulae:



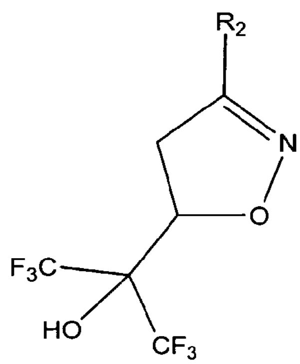
wherein E represents a heteroatom selected from O, S and N and R_2 is as defined.

17. A method according to Claim 16 having the following formula:

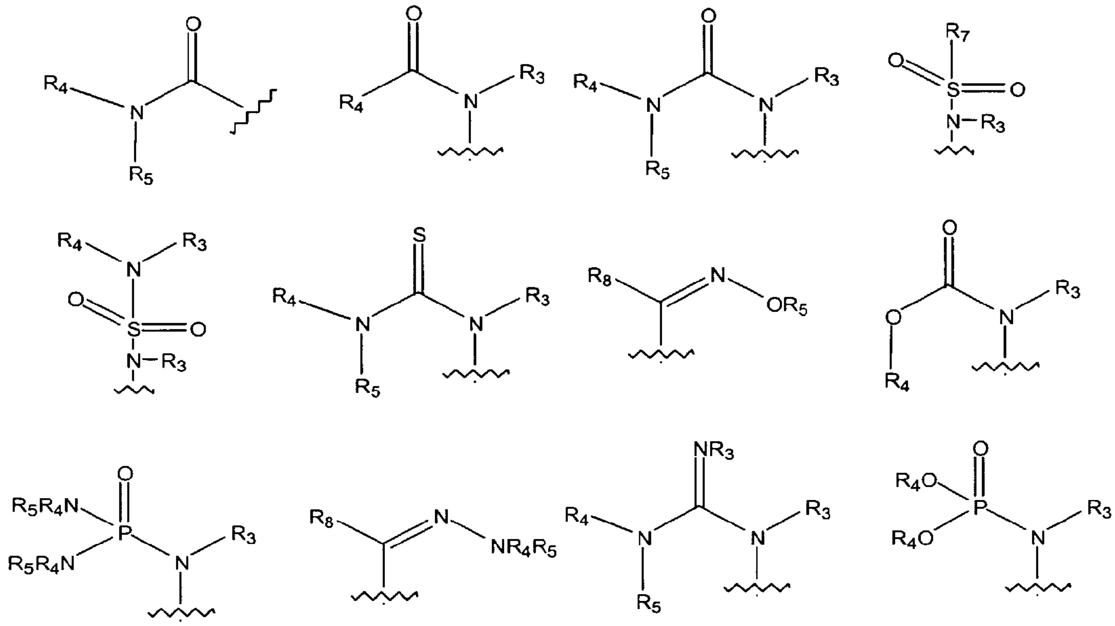


Wherein E is selected from N, O or S and R_2 is as defined.

18. A method according to Claim 17 wherein E is oxygen:

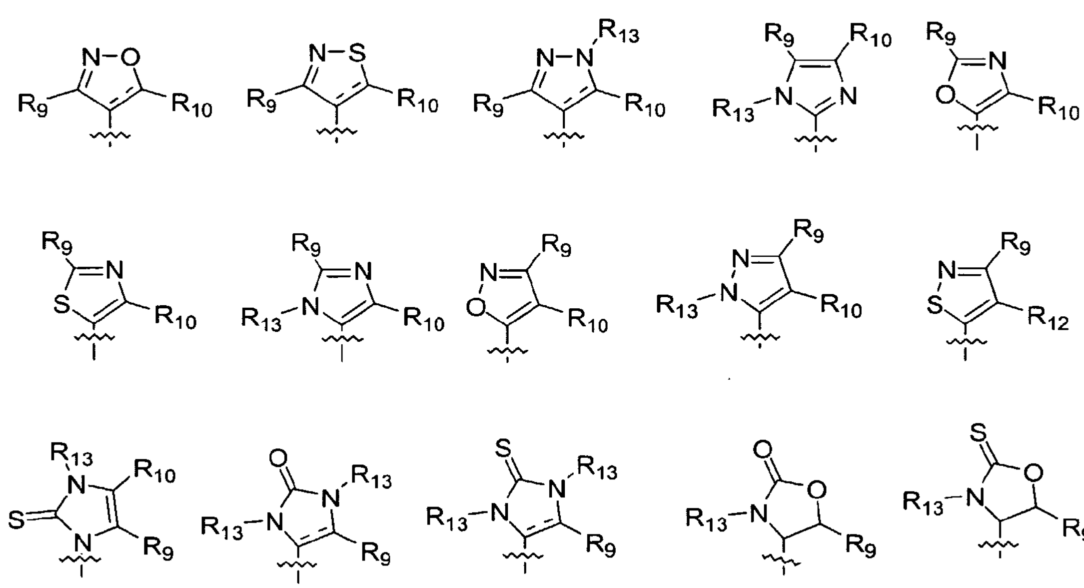


19. A method according to Claim 18 wherein R_2 is selected from the following groups:



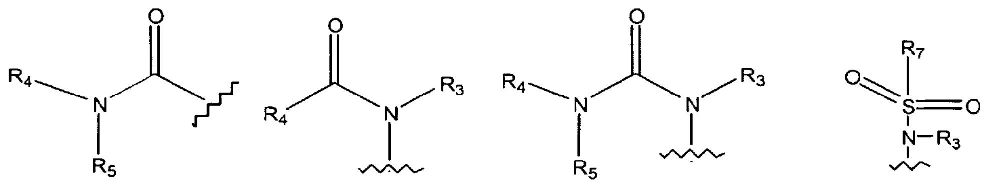
wherein R_3, R_4, R_5, R_6, R_7 and R_8 are defined above.

20. A method according to Claim 18 wherein R_2 is selected from a five membered heterocyclic ring containing two to three heteroatoms selected as follows:



wherein R_9, R_{10}, R_{11}, R_{12} and R_{13} are defined above.

21. A method according to 18, wherein R_2 is selected from the following groups:



wherein R_3, R_4, R_5, and R_7 are defined above.

22. A method according to claim 1 comprising the administration of a composition containing a compound selected from the group consisting of:

3-{[5-2,2,2-Trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-4,5-dihydro-isoxazole-3-carbonyl]-amino}propionic acid tert-butyl ester, 3-Methyl-2-{[5-2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-4,5-dihydro-isoxazole-3-carbonyl]-amino}-butyric acid tert-butyl ester, and N-Pyridin-4-ylmethyl-N-[5-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-thiazol-2-yl]isonicotinamide.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/12237

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P3/00 A61P9/00 A61K31/427 A61K31/422 A61K31/433 A61K31/34 A61K31/495 A61K31/035

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, FSTA, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 058698 A (CHUGAI PHARMACEUTICAL CO LTD ;CHEN MI (US); CHENG JIE FEI (US); HU) 1 August 2002 (2002-08-01) the whole document	1-22
P,X	WO 02 058690 A (CHUGAI PHARMACEUTICAL CO LTD ;HARAMURA MASAYUKI (US); BROWN STEVE) 1 August 2002 (2002-08-01) the whole document	1-22
P,X	WO 02 064136 A (CHUGAI PHARMACEUTICAL CO LTD ;CHEN MI (US); CHENG JIE FEI (US); HU) 22 August 2002 (2002-08-22) the whole document	1-20
X	US 6 316 503 B1 (HASEGAWA HIROHIKO ET AL) 13 November 2001 (2001-11-13) the whole document	1-13, 15-21

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2003	03/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Skjöldebrand, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 03705 A (TULARIK INC ;SHAN BEI (US)) 18 January 2001 (2001-01-18) the whole document	1-13, 15-21
X	WO 00 54759 A (TULARIK INC) 21 September 2000 (2000-09-21) the whole document	1-13, 15-21
A	SONG C ET AL: "Hypolipidemic effects of selective liver X receptor alpha agonists" STEROIDS, BUTTERWORTH-HEINEMANN, STONEHAM, MA, US, vol. 66, no. 9, September 2001 (2001-09), pages 673-681, XP004304415 ISSN: 0039-128X the whole document	1-22

INTERNATIONAL SEARCH REPORT	Inte onal application No. PCT/US 03/12237

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-13, 15-21 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-13, 15-21 (all in part)

Present claims 1-13, 15-21 (all in part) relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of these compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds in the examples and in claim 14 and 22.

Moreover, a "method for modulating liver X receptor (LXR)" is not considered a clear definition of a disease. The examination is therefore carried out for the use of the compounds of the generic formula (I) for the treatment of hypercholesterolemia and cardiovascular diseases.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/12237

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